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THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF THE NATIONAL TUBERCULOSIS ASSOCIATION

ABSTRACTS OF TUBERCULOSIS

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SILICOSIS AND ITS RELATIONSHIP TO TUBERCULOSIS[1,2]

LEROY U. GARDNER

Silicosis is that special form of pneumonoconiosis created by the inhalation of silica dust. It is of particular interest to the phthisiologist because it specifically predisposes to infection with the tubercle bacillus. In this respect it differs from most other known types of industrial dust.

It has been shown that silicosis is widely distributed throughout industrial populations and that it is not a medical curiosity, occasionally discovered in miners and quarrymen. Its prevalence and economic importance are now being emphasized by a deluge of damage suits in the courts of almost every state in our country. Frequently the claims are fraudulent; unscrupulous lawyers and physicians take advantage of the growing consciousness that dusty occupations may be harmful, to enrich themselves at the expense of industry. It behooves reputable members of the medical profession, and particularly those who specialize in diseases of the lungs, to familiarize themselves with this disease, for their advice will be sought with increasing frequency in the capacity of diagnostician or medicolegal expert.

The diagnosis of silicosis is established by a history of exposure to the inhalation of silica dust in occupation, by a roentgenological examination of the chest, and to a lesser extent by physical examination. An ideal occupational history would disclose the time and duration of exposure to dust, the type of that dust, its atmospheric concentration and the size and distribution of its particles. While all of these factors are not usually obtainable, a chronological tabulation of every occupation of the patient from the time since leaving school will usually suggest an exposure to dust, and inquiry from his employer will often disclose the type of dust in which he worked. Roentgenological diagnosis requires good films, expert knowledge and experience. The phthisiologist's general knowl-

[1] From the Saranac Laboratory for the Study of Tuberculosis, of the Edward L. Trudeau Foundation, Saranac Lake, New York.

[2] Presented at a joint session of the Clinical and Pathological Sections, at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 29, 1933.

edge of roentgenograms should suggest to him that some form of pneumonoconiosis exists, although until he has acquired experience he may require consultation to name its type and degree. The usual physical signs of pulmonary disease are surprisingly insignificant unless silicosis be complicated by infection.

Silicosis develops when a sufficient quantity of fine dust is inhaled over a sufficient period of time. The minimum dosage required to produce disease is unknown; but the condition is progressive, and clinical manifestations may appear years after discontinuing the exposure. Experiment has shown that the rate of reaction is proportional to the fineness of the dust. It is possible that other substances inhaled with silica may modify its action although this supposition lacks definite proof.

The inhaled particles reach the alveolar ducts and the alveoli leading from them where they are ingested by phagocytes. There is a decided tendency at first for pulmonary units situated beneath the pleura to be more heavily involved than those in the deeper portions of the lung. Phagocytes accumulate in considerable numbers within the lumina of these air-spaces, where they multiply actively and fuse together into compact plaques. Some of the cells are injured by the toxic silica and a variable number of polymorphonuclear leucocytes are attracted. The adjacent walls of the air-spaces are moderately thickened, owing to a proliferation of histiocytic cells which are the progenitors of more phagocytes. This reaction, which has been termed a *bronchiolitis* in South Africa, is a nonspecific response which develops as a feature of the reaction to most types of inhaled dust.

The characteristic lesion of silicosis does not appear until the particles have been transported by phagocytes, whose motility is specifically stimulated by the ingested silica, to the vicinity of the lymphoid tissues. Here these cells form a compact nodule, a "pseudotubercle," with the original lymphoid tissue at its centre. Local proliferation of the fixed tissue converts the primitive nodule into a mass of cellular connective tissue, and ultimately this undergoes characteristic hyaline transformation, with a loss of most of the nuclei. In the early stages of the disease such nodules develop almost wholly in association with the intrapulmonary lymphoid tissues and in the tracheobronchial lymph nodes.

The formation of nodules in these locations compresses the lumina of the lymph-vessels, and obstructs the normal flow of lymph. Elimination of particles which may be subsequently inhaled is thereby impeded. As a result, dust-cells do not remain within the lumen of the lymph-vessel

and reach their physiological destination in the tracheobronchial lymph nodes, but they tend to pass through the wall of lymphatic vessels and be deposited in the loose areolar tissue through which these structures course. A proliferation of connective-tissue elements in this location results in a fibrosis which is perilymphatic in distribution. Since the lymphatic trunks are situated in the walls of blood-vessels and bronchi, in the interlobular septa and the pleura, there is a progressive thickening of these structures.

The roentgenogram of the early case of silicosis, where the exposure to dust has been at all severe, reveals a diffuse haze extending inward from the lateral pleura of the midportion of the lungs. For unexplained reasons it is frequently more marked on the left side. Such a shadow is presumably cast by great numbers of superimposed minute foci of non-specific reaction in the subpleural air spaces ("bronchiolitis"). Accompanying this change there is a steadily increasing prominence of the linear markings in the lungs, due to perilymphatic fibrosis. Good stereoscopic films disclose a fine "beading" along the course and in the bifurcations of the trunks, the result of the formation of perilymphoid silicotic nodules. The shadow cast by the mediastinal elements is widened because of the enlargement of the tracheobronchial lymph nodes.

If the exposure to dust be continued the particles can no longer be eliminated effectively, and many of them are now carried directly into the alveolar septa. Here also they initiate proliferation, which results in a widespread fibrous thickening of these structures accompanied by the formation of circumscribed nodules. The latter at first develop about very small collections of lymphoid tissue in the peripheral portions of the bronchial tree, but it is probable that later some of them form at other points in the pulmonary framework. Since these peripheral nodules are not associated with the large trunks they tend to develop symmetrically, and usually attain a diameter of 2 to 3 mm. Except for the apices, they are distributed more or less uniformly throughout the lung. As the walls of the air-spaces thicken, their lumina seem to dilate sufficiently, so that they are readily visible to the naked eye. Along the borders and in the apices of the lung there is marked compensatory emphysema.

The roentgenogram now shows such a large number of nodular shadows that the previously prominent linear markings are obscured. The individual nodules are clean-cut and sharply defined because of the aeration of the emphysematous air-spaces about them. The mediastinal shadow

is still wide and even more dense. Any further advance in the disease is manifested by an increase in size and number of the individual nodules which may be so numerous as to permit practically no penetration of the rays. When confluent lesions are localized there is always suspicion of a complicating infection.

Recently much attention has been attracted by reports of "acute silicosis" developing after relatively short exposures of 12 to 18 months to heavy concentrations of pure silica. Such cases demand critical examination, in order to exclude the possibility of exposure to silica dust previous to the last occupation and to eliminate the complication of tuberculosis or other infections. Undoubtedly silicosis can develop in a relatively short time, for in guinea pigs the author has reproduced typical nodular disease in twelve months' time by 8 hours' daily exposures to concentrations of approximately 200 million particles per cu. ft. of air. Personal experience with human material has been limited to selected sections from 8 cases, which were submitted for examination. All of them showed reaction, either definite or suggestive, which was interpreted as due to complicating tuberculosis.

It would appear that, when the dust concentration is excessive, our normal physiological mechanisms are quite inadequate to eliminate the inhaled foreign particles. The phagocytes carry great numbers of the particles directly into all parts of the pulmonary framework and, in the general diffuse fibrosis which ensues, the preliminary obstructive lesions in the lymphatic system are quite overshadowed. Small hyaline nodules appear everywhere; cellular fibrous tissue thickens every portion of the pulmonary stroma; and the air-spaces contain dust-filled phagocytes in various stages of degeneration. In most of the cases thus far studied, typical caseous tubercles have been found in one place or another; in a few instances no definite tubercle has been detected, but a diffuse pneumonic exudation has complicated the picture. Frequently numerous cholesterol crystals are found within the necrotic exudate. Tubercle bacilli are rare or cannot be found at all. Unfortunately, in none of these cases was it possible to examine the entire lung to determine whether older localized tuberculous foci were present.

At least 75 per cent of those human beings who develop silicosis die of tuberculosis which may make its appearance at any stage of the disease. It becomes more frequent, however, in the more-advanced stages of silicosis. The infection may already exist in latent form when the individual takes up his occupation in the dusty industry, or it may be

acquired subsequently. In some instances it may not become manifest until years after the exposure to dust has ceased.

Animal experiments have demonstrated that partially healed primary foci of tuberculosis may be reactivated and rendered progressive by inhalation of silica. Serial roentgenograms of human beings exposed to silica have demonstrated reactivation of latent apical tuberculosis in the same manner. It seems probable that if either lesions contain living tubercle bacilli the dust will ultimately cause the lesions to become progressive.

There are many other cases in which the infection is assumed to have been acquired during occupational life. In them it is said that the first manifestation of tuberculosis appears not in the apex but in the middle or lower lung. The course of their disease may be either acute or chronic. In the silicotic experimental animal subsequent infection with attenuated tubercle bacilli tends to produce a rapid type of disease, which terminates fatally within three or four months. The nonsilicotic controls, on the other hand, practically never die of such infections. When the practice, accepted to-day, of employing in silica industries only men whose chest roentgenograms are normal, has been in force for some years the relationship between silicosis and the complicating infection should become more clearly defined.

The characteristic lesion of silicosis is modified by the presence of an active tuberculous focus in the lung, and possibly even inactive infections also exert a modifying effect. This applies not only to silicotic nodules in the immediate vicinity of the tuberculous area but to most of the other dust lesions in the lung. The individual nodules are no longer clean-cut and sharply defined, but their borders are irregular and extend as projections into the walls of the adjacent air-spaces. The centres of many of them are caseous, although tubercle bacilli are rare or entirely undemonstrable by staining methods. In the immediate vicinity of a tuberculous focus the nodules become very abundant and closely packed together. The extensions from their periphery form a solid matrix, which obliterates all air-spaces and binds together not only the nodules but the tuberculous lesions. Such an area is usually steel-gray in color and as hard and dense as heavy leather. Close inspection reveals the component nodules which may be somewhat lighter in color. Minute foci of caseation may or may not be detectable; cavity-formation is a late manifestation.

In the roentgenogram of silicosis complicated by early tuberculosis the

alteration in the character of the nodules is manifested by a peculiar fluffiness and haziness of their outlines. Furthermore, at some point in the lung the characteristic uniformity of distribution is interrupted and there is a marked tendency to aggregation of the nodules. When the process is far advanced the localized, massive, leathery fibrosis casts very dense shadows with ill-defined radiating borders. Often such changes are symmetrically located in the subclavicular or midportions of both lungs.

Numerous questions of greatest theoretical and practical interest are raised by the relationship which exists between silicosis and tuberculosis. No other known dust creates a specific susceptibility to such infection except possibly silicon carbide. This substance behaves similarly to silica in experimental animals infected with attenuated tubercle bacilli while other dusts do not. Satisfactory data for its action on human beings are not available. In the test-tube, silica added to artificial media definitely accelerates the initial lag period before tubercle bacilli begin to grow. This can possibly be explained by its buffering effect although other factors may be involved. In the body of an animal injected in one groin with silica and in the other with alumina or some other dust and then inoculated intravenously with tubercle bacilli, subsequent examination shows a great many more microörganisms in the local silica lesion than in that produced by alumina. Kettle believes that the specific necrosis produced by the silica offers a particularly favorable environment for the growth of the organisms. The Saranac Laboratory attenuated strain of tubercle bacillus, *R1*, regularly produces progressive tuberculosis in the silicotic animal. For a short time bacilli may be numerous in the pulmonary lesions, but soon they can only be detected by animal inoculation and yet the infection continues to progress, and ultimately terminates in death. The bacilli recovered and subinoculated into other nonsilicotic guinea pigs do not carry over their capacity to produce progressive disease, but excite only the localized lymph-node tuberculosis characteristic of this strain.

The fact that infection modifies the character of the silicotic nodule was observed in South Africa, and led the observers in that group to coin the term *infective silicosis*, by which they mean that the infection, though inactive, expresses itself in the character of the lesion. Some of the members of this group have even maintained that there could be no nodular silicosis without infection. This view is undoubtedly too extreme, for animal experiment has demonstrated that characteristic

nodules can be produced in the absence of infection. Nevertheless the mechanism by which a localized tuberculous focus can modify all the silicotic nodules in other portions of the lung is most intriguing. It may be some disturbance in the cellular immune reactions; it may be mechanical disturbance in the physiology of the lymphatic system.

The combination of silicosis and tuberculosis is a new condition, and not merely a combination or a superimposition of one process upon the other. The combined disease sometimes progresses rapidly and terminates fatally within a few months; at other times it is chronic in nature. Further study must determine whether the factors of immunity and dosage, of which we know something in simple tuberculosis, can be carried over with little or no modification to silicotuberculosis.

THE PREVALENCE OF SILICOSIS IN THE GENERAL POPULATION AND ITS EFFECTS UPON THE INCIDENCE OF TUBERCULOSIS[1]

A. J. LANZA[2] AND ROBERT J. VANE[2]

I wish to make it perfectly clear that there is little in this paper to justify its ambitious title. Silicosis is not a reportable disease. It is still commonly not diagnosed. Even in districts where it prevails, it does not appear on death-certificates to the extent which one might expect. Furthermore, such silicosis deaths as are reported are not separately classified by statistical offices using the *Manual of the International List of Causes of Death.* Lacking any definite statistical data upon which to make even a rough estimate of the prevalence of silicosis in the general population and its effect upon the incidence of tuberculosis, we can at best assemble some facts and figures,—statistical straws which may indicate how widespread is the exposure to silicosis, and how this exposure is reflected in insurance mortality statistics.

There are certain industries with which silicosis is associated as a major hazard and the number of persons engaged in these industries can be estimated with some degree of reliability. Then, in a great many other industries, there are isolated jobs or processes which may involve exposure to silica dust, but, as to the number of workers in these processes, we can do little more than hazard a guess. Mr. M. van Siclen of the American Institute of Mining and Metallurgical Engineers, in an excellent paper on *Health Hazards from Dust in the Mines and Allied Industries of the United States,* has presented carefully worked-out estimates of the number of workers exposed to silica dust in some of the major industries, using as a basis the 1929 censuses of mines and manufactures. We are indebted to him for many of the estimates used in this discussion.

ANTHRACITE-COAL AND METAL MINING AND QUARRYING

Our first thought naturally is of the metal mining industry. Conservatively figured, there are approximately 62,000 men engaged in this

[1] Presented at a joint session of the Clinical and Pathological Sections at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 29, 1933.

[2] Metropolitan Life Insurance Company, New York City.

industry who are exposed to a varying degree of silica dust. In anthracite-coal mining, there are about 145,000 men in the United States. Of these, about 2 per cent, according to the Pennsylvania Commission on Compensation for Occupational Disease, are more or less continuously occupied in drilling rock with jack-hammers, and this 2 per cent contributes a large portion of disabling miners' asthma, which, while commonly termed anthracosis, has a definite relationship to silica dust. There is a larger group of about 15 per cent of the anthracite miners who are mainly engaged in coal mining, but occasionally use the jack-hammer for drilling in rock. About 80 per cent are engaged almost exclusively in getting coal. Thus, of all the anthracite miners in the country, approximately 30,000 are exposed to silica dust. The quarrying of granite, trap-rock, slate, sandstone, diatomaceous earth, ganister, glass-sand, abrasive materials, millstones and the like comprise about 22,000 workers. In all, there are about 115,000 workers exposed to silica in these various types of mining and quarrying, a figure which, under present conditions especially, must fluctuate a good deal.

SELECTED MANUFACTURING INDUSTRIES

Next in importance after mining and quarrying, we should consider the chief manufacturing industries about which we have a few facts. Smelting and refining, both ferrous and nonferrous, employ about 18,000 men, whose jobs entail dust-exposure of varying severity. The foundries account for possibly 200,000 more. Potteries, glass-works, and plants manufacturing granite, slate and marble products employ respectively 35,000, 68,000, and 38,000 workers, of whom possibly as many as 50 per cent are exposed to silica dust. These would account for an additional 70,000. We come now to the incidental occupations with a real silicosis hazard, including grinders, numbering 27,000, buffers 35,000, and an unknown number of sandblasters and vitreous enamelers. Not all buffers and grinders, to be sure, are exposed to a silica hazard, and allowance must be made for those who are not.

Roughly, we should estimate the entire number in this group of manufacturing industries exposed to silica dust at 325,000 workers.

Summarizing the facts presented in the foregoing paragraphs and making allowances for duplications and omissions, it may be conservatively stated that there are approximately 450,000 workers exposed to silica dust in the chief mining, quarrying, and manufacturing industries. It must be remembered that there are probably a good many thousand

workers who have been exposed to silica dust in these various occupations and are now engaged in other forms of work.

OTHER INDUSTRIES OFFERING EXPOSURE TO SILICA DUST

The silica hazard, to be sure, is known to be present in mining and manufacturing industries other than those we have mentioned and in the building industry as well. Our survey would not be complete without giving some consideration to the large number of workers exposed to the hazard in these industries. Bituminous coal-mining, for example, employs 458,000 men, among whom, as among anthracite miners, are a number who are engaged in rock-drilling, and consequently are exposed to silica dust. Among the manufacturing industries with a more or less definite silica hazard, should be mentioned the making of abrasive wheels, sandpaper, hones and mineral earths, employing together about 8,000 men; the manufacture of mineral fertilizers, 21,000 men; of clay products (other than pottery manufacture) 93,000 men; and of cordage and jute-goods manufacture, 19,000 workers.

Many branches of construction work require considerable drilling in siliceous rock. In New York City alone, about 2,000 men at one time were employed at drilling, excavating, and blasting in rock containing a high percentage of free silica. Laborers and helpers in general construction and in road and street construction, together with steam- and street-railroad laborers and laborers in public service, many of whom are engaged in construction work, numbered 1,337,000 in 1930. It is in this class that most of the workers in the building trades exposed to silica dust will be found.

The combined total of workers included in this group of miscellaneous industries numbers about 2,000,000. In all probability only a small fraction of this total is exposed to the silica hazard. If, however, we apply even the conservative figure of 5 per cent as our estimate of those who would be exposed to the hazard, we shall have to add 100,000 workers to our general estimate.

Our very rough, but obviously conservative, estimate of the number of workers exposed to silica dust to a harmful degree in the United States is, therefore, upward of 500,000. We recognize that the data upon which this estimate is based leave much to be desired. Only the known exposures could be taken into account. The interesting thing about silicosis, which must not be overlooked in considering its importance in the nation's toll of ill health, is the unexpected places in which it is being

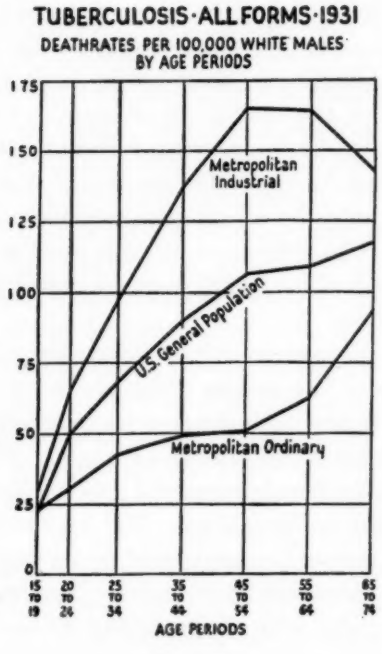
uncovered, and the revelations as to the extent of the damage being done in industries in which the hazard is known to exist.

What does the exposure of more than half a million workers to silica dust mean in terms of the prevalence of silicosis and of tuberculosis? We cannot, for the reasons given at the beginning of this paper, give a direct answer to these questions. Many competent students of industrial hygiene, as you are well aware, have shown an extremely high incidence of silicosis in those industries in which they have carried out thorough investigations. They have shown, too, how frequently silicosis terminates in tuberculosis. It is not our purpose to review these findings. Valuable as they are, they are entirely inadequate to serve as the basis for anything like a countrywide estimate of the number of silicotics. We think, however, that their findings, taken in conjunction with our estimate of persons exposed to silica dust, amply justify the assumption that, first of all, a very large number of industrial workers are the victims of silicosis, and second, that these silicotics contribute to the high incidence of tuberculosis and the high death-rates of industrial workers from this disease, especially at the later ages of life.

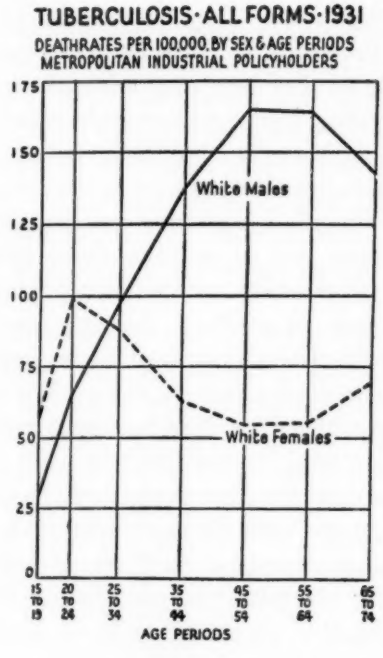
This latter statement finds partial support in certain mortality statistics made available to us. We present two graphs which are interesting in that they show the age-curve of tuberculosis death-rates for several population groups with varying degrees of industrial exposure. The graph on the right shows how the rates for female industrial policyholders compare with those of male industrial policyholders. The maximum female mortality, it will be noticed, occurs in the age-period 20–24 years, after which it rapidly declines to the age-period 55–64 years. The male mortality, on the other hand, rises rapidly with age, reaching its maximum in the period 45–64 years. At these ages, the death-rate for males is three times that of females, whereas at ages 20–24 the female rate exceeds the male rate by about one-third.

Graph 1, on the left, compares the mortality of three groups, all males, namely industrial policyholders, representing the greatest industrial exposure; ordinary policyholders, representing the least, with the males of the general population midway between. At each age, the lowest death-rate is shown for the ordinary policyholders, and the highest rate for the industrial policyholders. The disparity in rates increases rapidly with age from 15 to 19 years, when the rate for industrial policyholders is 28 per cent in excess of that for ordinary policyholders, to ages 45–54, when the industrial rate is three and one-quarter times the ordinary rate.

These differences may not be ascribed to industrial influences alone, least of all do they measure the effect of silicosis. The classes vary as to economic status for one thing, which, as has been well established, has an important bearing on tuberculosis mortality. The very considerable differences do, however, suggest the influence of silicosis, especially as the greatest disparity in the mortality rates occurs in those ages in which silicosis is most likely to show its effects.



GRAPH 1



GRAPH 2

More indicative of the direct influence of silicosis on the general deathrate from tuberculosis is a comparison of the mortality from this cause for men engaged in specific occupations with exposure to silica dust with the mortality for those not exposed. There is, unfortunately, in the United States no complete analysis of occupational mortality by which we might measure the effect of exposure to silica dust on the health and longevity of workers. The most recent data are found in an investigation made by twelve life-insurance companies into the occupational mortality of persons insured under ordinary policies (policies of $1,000 or more, payable quarterly or at longer intervals). The study

analyzes the mortality experience of those insured under policies issued during the years 1915 to 1926. The method employed was to compare the actual number of deaths, which occurred among men engaged in specified occupations, with the expected number of deaths on the basis of death-rates prevailing among standard lives of the same ages and for the same duration of insurance. Although these figures have been presented before, they will bear repetition.[3] It must be kept in mind that the standard of comparison is a group of selected lives insured under ordinary policies and not the general population. To offset this, however, it should be pointed out that the men in these specific occupations also underwent insurance selection. Table 1 shows the figures for occupations exposed to silica dust.

Table 1 bears out in a striking way what is implied by exposure to silica dust in terms of tuberculosis. The occupations showing the highest ratios of actual to expected deaths were, in order: underground lead- and zinc-miners, granite- and sandstone-cutters, copper-miners and gold- and silver-miners. All of these workers are exposed to a serious silica hazard. The ratios of actual to expected deaths from tuberculosis were, respectively: 1,833 per cent, 976 per cent, 913 per cent, and 804 per cent. There were actually 60 deaths from tuberculosis among these men as against six expected. Tuberculosis was responsible for one-half of all the deaths of lead- and zinc-miners, 29 per cent of the deaths of copper-miners, and 20 per cent of those among gold- and silver-miners. In all of these three mining classes, deaths from tuberculosis exceeded deaths from accidental injuries. Among iron-miners, who are, on the whole, probably less exposed to silica dust than are the other mining classes mentioned, we find that the ratio of actual to expected tuberculosis deaths is only 260 per cent. The ratio among quarry-workers was 263 per cent, 7 of the deaths being due to tuberculosis, while 2.7 might have been expected. It was impracticable to separate the granite-quarriers from the limestone-quarriers. If we had the figures, we should probably find that the excess among granite-quarrymen exposed to silica was much greater than among the limestone-quarrymen. This is clearly indicated by the difference in the mortality ratios for the granite- and sandstone-cutters and the marble- and limestone-cutters. The ratio of actual to

[3] *The Prevalence of Tuberculosis in Industry with Observations on the Dust Hazard:* a digest of a paper by Doctor A. J. Lanza and R. J. Vane, read before the Industrial Hygiene Conference, Chicago Tuberculosis Institute, April 25, 1930. Published in *Statistical Bulletin, Metropolitan Life Insurance Company, July, 1930, xi, no. 7.*

expected deaths among the former was 976 per cent, while among the latter it was but 294 per cent. There were 16 deaths from tuberculosis among the granite-cutters, as against 1.7 expected; whereas, there were 3 deaths in the limestone group, against 1 expected.

TABLE 1

Number of deaths expected from specified causes and number which actually occurred among persons engaged in certain occupations exposed to silica dust

Ordinary department mortality experience of twelve life insurance companies 1915–1926*

OCCUPATION	ALL CAUSES			RESPIRATORY TUBERCULOSIS		
	Actual Deaths	Expected Deaths	Percentage, Actual of Expected	Actual Deaths	Expected Deaths	Percentage, Actual of Expected
Metal mine operatives (underground)						
Gold and silver mines	44	9.77	450	9	1.12	804
Lead and zinc mines	22	5.03	437	11	0.60 (1)	1,833 (1)
Copper mines	83	22.63	367	24	2.63	913
Iron mines	33	12.12	272	4	1.54	260
Quarry operatives	37	22.45	165	7	2.66	263
Stone-cutters						
Granite and sandstone	29	17.47	166	16	1.64	976
Marble and limestone	12	10.55	114	3	1.02	294
Metal industries						
Grinders	46	28.65	161	7	3.33	210
Buffers and polishers	89	64.10	139	10	6.80	147
Chippers (not ship)	38	14.14	269	8	1.30	615
Core-makers and sand-moulders	32	22.65	141	3	2.92	103
Iron and steel foundries						
Moulders, founders and casters	202	130.14	155	24	13.38	179
Other operatives						
Drillers, flask-makers, machine-hands, mixers, etc.	45	31.03	145	7	3.03	231

* Compiled from *Joint Occupation Study—1928, Actuarial Society of America and Association of Life Insurance Medical Directors.*

(1) Approximate figure.

In grinding, another occupation in which there is exposure to silica dust, the ratio of actual to expected deaths was 210 per cent and there were 7 deaths from tuberculosis, as against 3.3 expected. Here, again,

we have a mixed hazard, for the sandstone-grinders, who work in the cutlery trade, have extreme exposure to silica dust and undoubtedly suffer inordinately from tuberculosis, whereas those who work on the composition wheels do not have this exposure and probably do not have very high rates from this disease.

The only other large occupational groups suffering exposure to silica dust included in the study are certain selected foundry occupations. An interesting feature of the foundry operatives' mortality, not brought out in the table, is that, while deaths from tuberculosis were higher than expected, extreme ratios are found for influenza and pneumonia rather than for tuberculosis. Dust is probably an important factor also in the high nontuberculous respiratory-disease rate. Chippers of metal had very high death-rates from both influenza-pneumonia and tuberculosis. There were 8 actual deaths from tuberculosis, as against 1.3 expected; and 17 deaths from influenza and pneumonia, as against 2 expected. Moulders, founders and casters had 24 actual deaths from tuberculosis, as against 13.4 expected; while there were 61 deaths from influenza and pneumonia, as against 23 expected.

There is another important question: What is the effect of silicosis in terms of tuberculous infection among other members of the family? Here again we are confronted by a lack of conclusive information. It has always been the impression among metal-mining communities, where silicosis is prevalent, that there is little tuberculosis among miners' families, even when the miner has died of silicotuberculosis. McFarland, and also Russell of the Public Health Service, have commented that in Barre, Vermont, the amount of tuberculosis among families of silicotics was less than among the general population, which they attribute in part to the comparatively late age at which the silicotics become tuberculous. However, Cummings of the Saranac Laboratory has kindly permitted me to quote some conclusions from as yet unpublished studies which he has made.

He studied a number of families of individuals with silicosis plus tuberculosis, the diagnosis being made by X-ray. He divided these into two groups, namely, sputum-positive and sputum-negative by guinea-pig inoculation. Over 50 per cent of the children under sixteen, living in contact with a silicotic having a positive sputum, showed X-ray evidence of tuberculous infection. Less than 30 per cent of the children under sixteen, living in contact with a silicotic having negative sputum, showed X-ray evidence of tuberculosis. All of the tuberculous infection shown

in these children was of the primary type; there were no cases of adult-type tuberculosis. Probably the situation with respect to tuberculosis among families of silicotics varies with the gravity of the silicosis hazard. When silicosis is severe and the individuals become tuberculous at a period when their children are small, there is naturally more likelihood of contact infection than when the silicosis hazard is less severe and becomes manifest at a later period in life when the children are older and have perhaps left the family circle. The whole field of family tuberculosis, in relation to silicosis, awaits careful investigation and study.

To sum up: There are sufficient data to indicate that, in the United States, the number of industrial workers exposed to the silica-dust hazard is in excess of half a million; that the mortality from tuberculosis among these persons is appreciably affected thereby; and that the extent of family infection due to silicosis plus tuberculosis is uncertain; but under some conditions, at least, it may be a serious problem.

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SILICOSIS IN GOLD-MINERS AND COAL-MINERS

Or Miner's Dyspnoea and Miner's Phthisis[1]

S. LYLE CUMMINS[2]

Long after the clinical condition known to-day as *silicosis* had been clearly recognized as occurring among metalliferous miners, it was still believed that coal-miners remained exempt from this disease. It was known that colliers had, in the past, suffered from respiratory trouble, but the whole trend of medical opinion was that this risk had almost or entirely been removed by modern improvements in the hygiene of the coal mines. Oliver, discussing this question in 1916 wrote: "Fifty years ago coal miner's phthisis or anthracosis was a well known disease; today, thanks to the well-ventilated condition of our mines, the malady has remarkably diminished in Great Britain." Haldane, in 1923, stated "that coal miners, far from being specially subject to the phthisis or other respiratory diseases from which the miners of Cornwall or the Rand suffer, are much less subject to these diseases than men in average occupations, although the dust breathed by coal miners contains much stone dust." He supported his statement by exhibiting a remarkable table (table 1) in which were contrasted the annual death-rates in England and Wales, for 1900–1902, per 1,000 living at each age-period from 15 to 65, for all occupied and retired males, coal-miners, and miners living in Cornwall, from which it was clearly evident that the Cornish miners, for the most part tin-miners, had a mortality from lung disease from five to seven times greater than that of colliers.

"It is difficult," Haldane says, "to resist the conclusion that in some way the inhalation of the dust in coal-mines tends to prevent phthisis." It will be noted, however, that, while Oliver speaks of "coal miner's phthisis or anthracosis," Haldane refers to the "phthisis" of metalliferous miners in Cornwall and in the Rand as "silicosis." This condition he defines elsewhere as "a disease of the lungs brought about by the inhalation of silicious dust and leading to tubercular infection of the lungs

[1] Presented at a joint session of the Clinical and Pathological Sections at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 29, 1933.

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accompanied by a great development of fibrous tissue in them." If Haldane's definition of "silicosis" be accepted, then his statistics must be admitted to prove that the coal-miner is free from silicosis. But it seems more reasonable, in the light of recent work on coal-miners, to prefer the definition of "silicosis" formulated by Irvine. "The term silicosis," he writes, "is to be interpreted as a condition of silicotic fibrosis of the lungs which is unaccompanied by a clinically detectable or overt tuberculosis." "Tuberculosis with silicosis is a condition of silicosis which is so accompanied." It is obvious that Irvine recognizes as silicosis a stage of pneumonoconiosis which is uncomplicated by tuberculous infection, while Haldane prefers to reserve the word for cases of miner's phthisis only, in which the infectious element has been added.

TABLE 1

Annual death-rates, England and Wales, 1900–1–2, per 1,000 living at each age-period

	AGE 15–20		AGE 20–25		AGE 25–35		AGE 35–45		AGE 45–55		AGE 55–65	
	Lung disease	All causes	Lung disease	All causes	Lung disease	All causes	Lung disease	All causes	Lung disease	All causes	Lung disease	All causes
All occupied males.....	0.8	2.2	2.0	4.4	2.8	6.0	4.4	10.2	6.3	17.7	8.7	31.0
Coal-miners.....	0.7	3.2	1.4	4.5	1.6	4.9	2.4	7.6	4.8	14.7	12.0	36.0
Miners living in Cornwall.....	0.7	1.7	2.7	5.8	17.3	20.9	33.2	39.0	32.2	44.6	42.6	70.5

It is clear that we have to take into account two separate pathological pictures, "silicotic fibrosis" and "tuberculosis with silicosis;" and two separate clinical states, "miner's dyspnoea" and "miner's phthisis." The dyspnoea depends upon the silicotic fibrosis and the phthisis or wasting depends upon the tuberculosis. The epidemiological difference between silicosis of the South Wales coal-miner and that of the South African gold-miner lies simply in the fact that the coal-miner, though probably more liable to dyspnoea, is far less liable to phthisis than the gold-miner. He gets silicosis but, for some reason, he appears to stop short of phthisis in the majority of cases. But what is "silicosis"? Irvine calls it a "silicotic fibrosis of the lungs." It is obvious that a silicotic fibrosis must mean a fibrosis induced by silica; but must the silica be free silica or should we apply the term silicosis to a fibrosis induced by a silicate? Badham (1927) holds that there is a fine type of fibrosis due to silicates and suggests for it the name of *silicatosis*. This is too easy a line of

nomenclature to commend itself for general adoption at the present time. The fact is that in spite of the definitions suggested by the Johannesburg Conference of 1930, we do not yet *know* for certain whether the classical silicosis of the Rand depends only upon free silica or partially or wholly on some other constituent of the Rand dust. Watkins-Pitchford and James Moir (1916), after a careful study of the mineral particles in the lungs of silicotic miners, prefered to keep an open mind on this point. "It has become obvious that not only amorphous particles of quartz but also particles of other moderately hard and insoluble minerals are liable to be carried into the lung tissues—whether they are equally deleterious is, however, one of the problems of the future."

We have a rather precise concept of silicosis as a clinical and pathological entity, but as to the essential problems of aetiology, our information is by no means so securely established. For those who have set themselves the task of investigating the problem of dust diseases in industry, there still remain unsolved three fundamental questions which are as follows:

1: Is "silicosis" caused by free silica only or by some other mineral associated with the free silica in the dust of hard stone?
2: Is "silicosis" the result of mechanical irritation by insoluble dust particles retained in the pulmonary and adenoid tissues or is it caused by the solution of fine dust particles and the physicochemical action of the resulting sol or gel?
3: Is the pulmonary tuberculosis so frequently associated with "silicosis" to be attributed chiefly to the activation of preëxisting tuberculous lesions by silica and its products or rather to the effects of lymph stasis and fibrosis in favoring superinfections?

These three questions are so closely linked that it is impossible to approach any one of them without raising all the others.

By most observers, the writer included, it has until quite recently been tacitly assumed that "silicosis" was caused by inhaling free silica in fine division. This conclusion seemed justified by the fact that it was precisely those dusts known to be derived from rock containing a very high proportion of free silica which were most dangerous; by the finding of minute bright particles believed to be free silica in the lungs of "silicotics"; and by the high percentage of silica proved by chemical analysis to exist in the ash of silicotic lungs. However, Watkins-Pitchford and James Moir, in their paper (1916), *On the Nature of the Doubly-Refracting Particles Seen in Microscopic Sections of Silicotic Lungs*, made it clear that

gold-miners were inhaling and retaining in their lung-tissues not only the pure dust of free silica but a mixed dust consisting of various doubly-refracting mineral particles, quartz, sericite, rutile and so forth. "It is almost certain," they say, "that a large proportion of the bright white images which are seen by polarized light in a silicotic lung section *of Rand origin* are produced by sericite." The "banket" at Johannesburg is stated to contain about 90 per cent of free silica, but it is not safe to assume that free silica is its only noxious element. Watkins-Pitchford and Moir figure their findings in a crushed fragment of banket matrix, and say of it that "the sericite fragments in this particular specimen of matrix were actually more abundant than the quartz particles."

These early observations, which struck a note of caution, appear to have been, to some extent, ignored in later work. At the International Congress on Silicosis held at Johannesburg in 1930, silicosis was defined as "a pathological condition of the lungs due to the inhalation of silicon dioxide." The subject has recently been reëxamined from the petrological point of view by Dr. W. R. Jones of the Royal School of Mines, London. Jones studied, in the first instance, the mineral constituents of the rocks drilled in various industries, comparing the banket of Johannesburg, where "silicosis" is common, with the silicious rock of the Kolar gold-fields where the disease appears to be rare or absent; and he compared the hard rocks of the South Wales Coal Measures, where much silicosis occurs, with those of the Scottish coal-fields where silicosis has not, so far, been noted as common. In the Rand banket and in the rocks and shales of South Wales, he found sericite to be present in great quantities as a numerically vast collection of minute fibres in between the quartz particles. In the matrix from the Kolar gold-field, the quartz particles were found to be in close apposition, edge to edge, without any sericite fibres between; and sericite was absent, also, in the rocks from the Scottish coal-mines. Where "silicosis" was common, there sericite was present; where silicosis was absent, there was no sericite.

Jones now turned his attention to the mineral constituents of human lung; and here his work promises to be of great pathological interest. He has been kind enough to allow me to communicate the salient facts in advance of his publication in the *Journal of Hygiene* for July, 1933. His conclusions, based on the examination of the mineral residues obtained from 29 silicotic lungs, and of the examination of the rocks and materials which gave rise to the inhaled dusts that caused these cases of silicosis, are given in his own words as follows:

(1) The bulk of the mineral residues obtained from every silicotic lung investigated by the author consists of minute fibres of the mineral, sericite, a hydrated silicate of aluminium and potassium known also as "secondary white mica." This mineral is abundantly present also in all the rocks and materials which gave rise to the inhaled dust that caused these cases of silicosis; and it is present in these in minute fibres and scales of the size it is found in the residues and also in the lung tissue.

(2) Silica in the uncombined state, as quartz, is also present in these residues as relatively coarse and fine grains; it is however, in amounts subordinate to sericite, and very markedly so with regard to the number of quartz particles compared with the countless fibres of sericite.

(3) One relatively large grain of quartz, measuring 10 x 8 x 5 microns such as is found in the residues, is equal in volume to 800 fibres of sericite measuring 2 x 0.5 x 0.5 microns, and contributes as much silica in the chemical analysis of a residue as would 17,021 such fibres of sericite. The author suggests that this is out of all proportion to the silicotic effect of one such quartz grain compared to the effect in the lungs of hundreds of fibres of sericite.

(4) Silica in the uncombined state, as quartz, is not mainly the cause of silicosis in these and certain other cases. This appears to be conclusively established, the author submits, by the following facts (a) the amount of quartz and the size and form of the quartz grains in the sandstones occurring in the underground working-places in the Scottish coal-fields and in the South Wales coal-field are alike. The latter sandstone gives rise to dust that has caused scores of cases of silicosis whereas not a single authenticated case of silicosis has been produced in the Scottish coal-fields. (b) The gold-bearing quartz-conglomerate of South Africa gives rise to dust that has caused thousands of cases of silicosis; the gold-bearing quartz rock of the Kolar gold-field, India, contains more quartz than the South African rock and yet produces dust that has never caused one case of that disease. (c) No quartz-bearing rock investigated by the author which does not also contain abundance of fibrous aggregates of sericite or of fibrous silicate minerals, loosely held together and easily freed into the atmosphere when the rock is drilled and blasted, is known to have given rise to dust that causes silicosis. (d) Rocks which contain a relatively small percentage of quartz (well below the minimum amount in the rock types named in the Silicosis Schemes under English Law) but which do contain fibrous silicate minerals such as sericite and sillimanite, as for example, at Broken Hill Mines, New South Wales, produce dust that has caused a large number of silicosis cases.

(5) These investigations are not concerned with the pathological condition produced in the lungs by the minerals. Whether they merely act as mechanical irritants causing the growth of fibrous tissue as advocated by some well-known authorities, or induce chemical changes, as maintained by other eminent

pathologists, is a question entirely beyond the province of the author. His conclusions do not militate against either theory; on the contrary, they provide the former school with evidence of the presence in the lungs of thousands of acicular fibres that presumably could act as mechanical irritants, and the latter school with evidence of the presence of silicate minerals less stable than quartz and which, due to their physical form, expose far greater surface to volume for any chemical action than do the more compact grains of quartz.

(6) Lastly, the author's case is that it is mainly the presence in the exploited rocks and materials of *fibrous minerals*, be they sericite, sillimanite, tremolite, asbestos, etc. (or even a fibrous form of free silica, or of a fibrous rock like pumice) in aggregates which during the impact of drilling, blasting, or crushing, become freed into the atmosphere as individual fibres, that enables sufficient material in course of time to enter the lungs to cause silicosis. He does not maintain that sufficient minute particles of quartz could not, under any circumstances whatever, enter the lungs to cause silicosis although the cases he has hitherto investigated appear to show conclusively that they have not done so; but he does maintain that the fibrous minerals hasten the process so very considerably that their presence in the exploited rocks and materials is of far greater importance in causing this disease than is the presence of quartz.

It is as yet too early to decide whether Jones's theory is right or wrong. All that can be claimed at present is that the known facts of "silicosis" fit as well into the "sericite" hypothesis as into the theory of "free silica." His suggestions do not invalidate, but may help to explain, the findings of the pioneers in the production of experimental "silicosis" in animals by means of quartz dust. Mavrogordato, Gardner, Kettle and others have proved experimentally that quartz dust, inhaled into the lungs of laboratory animals, produces the characteristic nodular fibrosis which has been described in man as silicosis. Their experiments are invaluable in demonstrating the dangerous properties of the dust from certain types of rock or other material and thus indicating a line of prophylaxis; but the dusts used in these experiments have in most cases contained *mixed* constituents, not pure or isolated minerals. Future experiments must be performed with the latter.

To turn for a moment to the second question of those cited above as still unsettled; what of "mechanical irritation" as opposed to the "solution of silica" theory in the production of silicosis? It may be said at once that Jones, in raising the question of sericite, makes no attempt to settle this solubility problem, merely pointing out that sericite is better calculated than free silica to fit into either theory—a smaller more penetrating

particle to produce mechanical effects or a larger surface of a rather more soluble mineral available for the action of the tissue juices!

Our position, as medical men, in search of an explanation of a pathological problem, appears to be roughly as follows:—Collis and others have suggested that a theory of solution of free silica and its chemical action fits in better with the facts of "silicosis" than the older theory of mechanical irritation. Gye and his co-workers have proved that silica sol, produced by the action of hydrochloric acid on "waterglass," a solution of sodium silicate, has toxic properties, can produce fibrosis in certain organs when injected intravenously, and accentuates the local multiplication of tubercle bacilli and other bacteria in the tissues. We have reason to think, therefore, that free silica, if it does go into colloidal solution in the lungs, might be expected to produce just those toxic, fibrogenic and tuberculoadjuvant effects which are observed in "silicosis." But we have not yet proved that it does go into solution in the tissues. Chemists often express surprise that we have chosen for this theory the most insoluble of minerals; but the "solution" hypothesis is much easier to defend if, as suggested by Jones, "silicosis" depends upon minute particles of sericite and other fibrous silicates, substances more soluble than uncombined silica.

The observations of Belt (1929) and others to the effect that the bright particles seen in sections of silicotic lungs are much more numerous at the periphery of nodules and tend to be rare or absent in the older central fibrotic areas go far to support the theory of slow surface solution of the mineral particles and suggest the conversion of the inhaled dust to occult silica in those parts where the bright particles are absent. To the writer, the truth of the "solution" theory appears more than probable; but it cannot yet be regarded as finally established. In the case of large silicate particles, such as asbestos fibres, and in the case of certain large crystalline or fibrous particles of indeterminate nature found in the lungs of coal-miners, it is easy to see around them the accumulation of a deposit or accretion of foreign material in the shape of an annulated or tufted sheath constituting the "Curious Body" of Cooke, Tylecote and Dunn, and other observers; an appearance which implies interaction between fibre and the tissues; an interaction which, perhaps, suggests some degree of surface solution and gel formation. What goes on around the minute fibres of sericite and other minerals, so small as to approach the limit of visibility, we can so far only guess; but it seems almost certain

that some degree of solution must take place. The work of Landsteiner has shown what curious physical effects belong to silica sol in contact with the cells and humors of the tissues and blood; and the experiments of the writer and C. Weatherall suggest that the agglutination of the dust-cells in the lung tissue noted by Mavrogordato as a preliminary stage in nodule-formation may be brought about by the silica sol formed in and around these phagocytic cells.

Although absolute proof of the "solution" theory is lacking, the evidence in favor of it is so strong as to justify us in making use of it as an approach toward the discussion of the third problem, the question of whether "silicosis predisposes to 'phthisis' through the activation by dust of preëxisting tuberculous lesions or by the facilitation of superinfection through the mechanical effects of fibrosis and lymph-stasis." Animal experiment suggests that silicosis may act in both ways. The beautiful experiments of Gardner (1929) in the "dusting" of guinea pigs previously infected with latent R1 tuberculous lesions appear conclusively to prove that smouldering tuberculosis may be fanned into activity by quartz dust; while the work of Kettle in proving that tubercle bacilli injected into the circulation of mice and rabbits tend to settle in the localized subcutaneous lesions produced by silica, together with the experiments of Gardner (1920) and his co-workers in causing "dusted" animals to inhale R1 tubercle bacilli, indicate that the occupation of the tissues by dust facilitates tuberculous invasion. But when it comes to the problem of miner's phthisis, we find that the experimental findings in animals fit in badly with the observed facts. "Tuberculosis is in the great majority of cases a terminal phenomenon, attacking the sufferer from fibrosis when that condition is already advanced,"—this is the opinion of Watt and Irvine (1912) and it has been fully borne out by subsequent observations. If there occurs in human pneumonoconiosis any early activation of latent tuberculosis by quartz dust such as has been proved to occur in R1 guinea pigs by Gardner, an example may, perhaps, be found in the rapidly developing acute generalized tuberculosis in young African natives arriving at the Rand gold mines from villages where tuberculosis is now endemic. That silicious dust plays a part in this phenomenon can hardly be doubted; but here it is only one of several "factors of aggravation" and its exact importance is difficult to ascertain. We know that a very similar type of early fatal generalized tuberculosis arises in the South African diamond mines, the Witbank coal mines and even in the South African Native Mental Hospitals; in other words, that

it is, to a great extent, the expression of a low resistance to tuberculosis; and that it occurs not only in those natives exposed to silicious dust, but also, though to a less extent, in natives not so exposed. The above possible exception apart, it may be stated as a fact of general application that, in the pneumonoconiosis of miners, "phthisis" is a terminal phenomenon; that it is preceded by a considerably prolonged period of silicotic lung fibrosis and dyspnoea; and that this latter is, itself, preceded by some years of gradually increasing lung fibrosis unaccompanied at first by any considerable dyspnoea or other untoward symptom. It seems clear that the human lung can accumulate silicious dust over many years without becoming actively tuberculous; that the first effect of silicious dust—a very slow one—is fibrosis; and that phthisis, if it supervenes, must be the result of superinfections, either exogenous or endogenous in origin, reaching the lung simultaneously with or subsequently to the silicious dust. Observers, like Beattie (1916), who have studied the histological side of the problem in human lungs seem to be unanimous in thinking that the tuberculosis assumes a more than usually fibrotic type in the presence of silicosis; and that the silicotic fibrosis is accentuated by the presence of simultaneous tuberculous infection. It looks as if the silicosis, while undoubtedly adding to the risk of a terminal tuberculosis, actually retarded rather than hastened the tuberculous process itself. The writer, when Gye first proved the adjuvant effect of silica sol on the local pullulation of tubercle bacilli, was inclined to explain this through the antibactericidal action of a colloidal solution, such as he was able to demonstrate when silica sol was added to a mixture of lytic blood and typhoid bacilli. Further work failed to demonstrate any lytic action of blood or serum on tubercle bacilli, nor was it possible to show any increased rate of growth of tubercle bacilli in either blood or serum to which colloidal silica had been added. Subsequent experiments, a report of which is to appear in the *Journal of Hygiene* of July, 1933, have confirmed the observations of Gye and of Kettle that the inoculation of silica sol along with tubercle bacilli is followed by a demonstrable excess of tubercle bacilli at the site of entry for some days after inoculation; but that this may depend, in part at least, upon their retention locally by the inflammatory reaction produced by the silica. It is difficult either to deny or to assert that more rapid growth of tubercle bacilli takes place, although there is no doubt whatever that more bacilli can be *seen* in the lesions caused by silica sol and tubercle bacilli together than in those due to tubercle bacilli alone.

On these grounds, the writer is more inclined to attribute the high tuberculosis mortality in the late middle-age periods in gold miners, and other workers exposed to silicious dust, to the *accumulation* of inhaled tubercle bacilli in the fibrotic lung than to a direct adjuvant action of dissolved silica. Tubercle bacilli, like other particles inhaled into a lung the lymphatic drainage of which is blocked up by silicotic fibrosis, must necessarily accumulate therein; and, although their spread is restrained by fibrosis, they may be expected to exert a definite pathogenic and toxic effect in their immediate vicinity; an effect which may only attain to the clinically recognizable threshold after the lapse of years. On this hypothesis, the effects of silicious dust in the activation of phthisis, except, perhaps, in a small number of young adults with active but larval lesions,

TABLE 2

Mean annual death-rate: respiratory tuberculosis per 100,000

	TOTAL CASES	AGE 16–	AGE 20–	AGE 25–	AGE 35–	AGE 45–	AGE 55–	AGE 65–	AGE 70–
All occupations and retired miners	48,357	69	136	133	160	166	150	114	64
Slate-miners and quarriers	51	—	53	188	195	307	491	727	91
Metal grinders	231	61	136	237	551	1,149	1,246	761	388
Tin- and copper-miners not surface staff	102	—	91	746	1,520	1,744	2,632	517	680
Sandstone-masons, cutters and dressers	167	356	—	67	468	1,084	1,081	895	77
Coal-hewers and getters	1,486	40	78	80	110	114	139	147	47

are indirect; and are brought about by the fibrosis and lymph-stasis rather than directly through some physicochemical action on the tubercle bacilli.

The important point is, however, that, whether by direct or indirect action, the inhalation of a silicious dust favors the progress of tuberculosis as a terminal complication of pneumonoconiosis. In the words of Mavrogordato (1926), "There is no doubt that dust facilitates tuberculous infection, otherwise there would be no such thing as phthisis-producing dust; and tuberculosis without tubercle bacilli is impossible." But if the dust from silicious rock favors tuberculous infection, how is it that, while the metalliferous miners on the Rand and in Cornwall and other places exemplify this truth by showing an exceptionally high tuberculosis death-rate in late middle age, the South Wales coal-miners, a group of workers exposed to the dust of hard rock and proved to be liable to a

form of silicotic fibrosis with the closest clinical, X-ray and pathologico-chemical resemblances to the silicosis of the Rand, seem, from the Registrar General's records, to be quite exempt from the risk of "phthisis"? Although we have no occupational statistics for South Africa at all comparable to those kept by the Registrar General in Great Britain, we are able to state without equivocation, from the records of the Miner's Phthisis Bureau, and from the excellent graphs in his *Studies in Experimental Silicosis* by Mavrogordato (1926), that "primary" and "anti-primary" silicosis lead on, in the case of the Johannesburg silicotics, to "secondary" silicosis in most cases and, finally, to fatal "phthisis." We are not in a position to make a direct comparison between these Johannesburg silicotics and our South Wales coal-mining silicotics because we, in South Wales, lack the kind of statistics which are collected at the Miner's Phthisis Bureau, while they, in South Africa, are without the comprehensive occupational statistics which are kept up officially for all industries in England. We can, however, compare the mortalities, either general or special, in coal-miners and in those industries in which a special silicotic risk is known to occur.

From this comparison, it is quite clear that the coal-miner has no greater liability to death from recognized and recorded "phthisis" than the standard group of "all occupied and retired males." It is equally clear that there is a marked and, in some of the "dusty" industries, an appalling risk of terminal "phthisis." How does the coal-miner, known to be liable to silicosis, escape? There are two possible explanations:

(1) He escapes because his lung fibrosis is not the true phthisis-producing silicosis of the Rand but only a "silicatosis" with no "phthisis" risk.
(2) He seems to escape because the coal dust so modifies and detoxicates the phthisical lung lesions that the condition of tuberculosis, though present, escapes recognition and is therefore absent from the death reports on which the Registrar General's statistics are based.

As to the first explanation, the new ideas about silicosis in general, put into circulation by Jones's recent work on sericite, have to be borne in mind. It is at least possible that the silicosis of the Rand may be due, in whole or in part, to the minute dust of sericite fibres inhaled along with the quartz dust. There appears to the writer to be a very strong case for sericite as the dangerous element in the dust of the South Wales coal-mines. Sections of silicotic lungs from Welsh coal-miners have been submitted to Dr. Jones, who, in the course of examination of the sections,

and of corresponding lung residues, with the petrological microscope, has recognized the bright particles present as, for the most part, sericite. It has been shown by the writer and Dr. Sladden that the extent of lung damage and fibrosis in Welsh miners varies directly with the total amount of silica, expressed as SiO_2, present in the lungs, and with the number of "bright particles" of a certain type seen in the sections on examination with crossed prisms. To put this latter point to the test, the writer recently arranged to have 59 sections from lungs of which a chemical analysis was available sorted out and relabelled in such a way that he should not know what section he was examining. All these sections were examined with crossed prisms and were divided into four lots according to the number of bright particles present; and the findings were subsequently coördinated with the chemical reports as to the percentage of SiO_2 in the ash. The results were as follows:

Total sections	*"Bright particles" visible in sections*	*Average SiO_2 of ash*
9	+++	32
17	++	27
18	+	15.3
15	−	2.8

While the exact significance of "bright particles" is admittedly difficult to determine, it may be said that the type of bright particle accepted by the writer in this study, and at that time believed by him to represent silica particles, was exactly that which has since been recognized by Jones as undoubtedly sericite. It looks then as if the chief source of the silica found to be present in coal-miners' lungs, and once more conclusively shown by Sladden in a recent report (1932) to vary directly in amount with the degree of lung damage, was not necessarily free silica but more probably combined silica in the shape of sericite. Further analyses, in which account must be taken of the amount of aluminium and potassium in the lung tissue, are necessary to establish this point. It may be added that an examination by the writer of sections of South African silicotic lungs showed, as the most numerous type present, bright particles indistinguishable from those of the South Wales cases recognized by Jones as sericite.

While, therefore, it is very probable that the harmful element in the dust in South Wales is, to a great extent, a silicate, this may well be equally true of the dust which leads to silicosis and phthisis on the Rand. The plea that phthisis is relatively rare in Wales because the pneumono-

coniosis is not true silicosis cannot yet be accepted as valid in the light of such facts as we now possess.

The second explanation, that the coal miner *seems* to escape terminal tuberculosis because, in the words of Haldane, "in some way, the inhalation of the dust in coal mines tends to prevent phthisis," appears to be a much more promising line of argument and deserves serious consideration.

"*Seems* to escape." Is this apparent exemption of the coal-mining industry a real phenomenon or only one of those statistical conceptions which hover like mists around the mathematical expert who has to depend for his material on records compiled from medical notifications? All who have worked in a coal-mining district know that individual coal-miners often develop severe pulmonary tuberculosis. It is only in the comparative study of large groups that the alleged exemption of colliers from any undue mortality from phthisis comes to light. A recent Report, *Technical Paper 545*, by R. R. Sayers, F. V. Meriwether, A. J. Lanza and W. W. Adams, published by the U. S. Bureau of Mines, would seem to show that a comparison between coal-miners and other hard-rock miners elicited no significant difference in respect of incidence of silicosis and of silicosis complicated by tuberculosis. Here the men examined appear to have been insured persons and the examination, like that at Johannesburg, was carried out by the same examiners on persons willing to submit themselves to medical referees. It is quite possible, nay, probable, that a similar examination of South Wales coal-miners would reveal a somewhat similar picture; but no similar examination has yet been carried out. Individual investigators have, however, supplied some significant information. Of 127 "healthy" miners, a selected group with not less than 20 years' work at the coal-face, examined by the medical staff of the Welsh National Memorial Association, over 50 per cent showed "mottling" on X-ray examination. Of 100 old retired coal-miners examined by Dr. Enid Williams, a research student in the Tuberculosis Department at Cardiff, 6 per cent proved to have tubercle bacilli in the sputum; and over a fifth of those examined exhibited a blood picture suggestive of the disease. It looks as if a comprehensive examination of South Wales colliers might show unexpected features. Judging from the pathological and histological findings of Cummins and Sladden, it is to be expected that radiological examination of colliers still at work and in good general health would reveal a rather high proportion of men with the "generalized mottling" regarded in South Africa as indicating the "anti-primary" and "primary" stages of silicosis; and it is not un-

reasonable to guess, in view of the findings of Enid Williams based on a single sputum examination, that a periodical examination of the sputum of large groups of men now working at the coal-face might show an unexpectedly large number of "positives." But while all this is so likely, the fact remains that the colliers, as a class, do not exhibit any marked tendency to a recognized "phthisis" as a preponderating element in the death-returns. By "phthisis" the writer means "phthisis" in the Watkins-Pitchford sense of the term; that is to say, "an active tuberculous process." "Phthisis" in this sense is an easily recognized condition and one not likely to be missed by the attending physician in the last hours of the patient's life, on which the death-certificate is based. The comparison on which the writer bases his belief that the colliers, as a class, are relatively exempt from a terminal "phthisis," such as was regarded by the Royal Commission on Metalliferous Mines and Quarries (1914) as characteristic of those "exposed to the inhalation of injurious dusts," is that of the Registrar General's figures, already quoted, in which it is shown that, while colliers exhibit a mortality from pulmonary tuberculosis rather less, in all age-groups, than "all occupied and retired males," the tuberculosis mortality of the several industries involving exposure to silicious dust without simultaneous exposure to coal dust is appallingly high. If the certifying doctors are able to recognize and record this terminal "phthisis" in Cornwall and other places, the certifying doctors in the Welsh valleys would recognize and record it too. The fact is that the majority of the old retired Welsh colliers are in good muscular condition and quite unlike the picture called up by the word "phthisis." The one outstanding feature of these old men is *dyspnoea;* the one obviously appropriate diagnosis is *bronchitis*. And, as will be evident from table 3, taken from the *Report of the Medical Staff of the Welsh National Memorial Association*, already referred to, it is the diagnosis of "bronchitis" which is entered upon the death-certificate of the old coal-miner when some chill or catarrh raises his dyspnoea to the intolerable threshold of oxygen starvation which closes the scene.

What is the relation, if any, of this terminal "bronchitis" of the coal-miner to the terminal "phthisis" of the gold-miner? Both conditions depend on, or supervene upon, a state of pneumonoconiosis. The "phthisis" of the metalliferous miner seems to lead to a slightly earlier death; the fatal "bronchitis" of the collier is chiefly visible in the decennia 65 and 75. So late in life is this terminal bronchitis that the question arises whether the old collier dies *of* bronchitis or merely dies *with* "bron-

chitis," a death from old age and general failure being attributed to the dyspnoeic condition which had characterized the patient for many years. This is a point which need not be labored. The problem of real importance is why the silicotic coal-miner, dyspnoeic and with his lymphatic lung drainage out of order, still manages to escape, for the most part, the "phthisis" which so often leads to a rather earlier death in the metalliferous miner.

It is natural to examine, at this point, into the outstanding pathological and histological differences, if any, between the lungs of the collier with

TABLE 3

South Wales coal-miners

Coal-Hewers

	AGE-PERIODS							
	16–	20–	25–	35–	45–	55–	65–	75–
Bronchitis								
Monmouthshire	—	5	—	20	74	255	1,235	3,053
Glamorgan	—	2	3	16	83	508	1,304	3,542
*Western Area	—	—	—	24	59	789	4,138	5,936
All occupied and retired males	1	3	6	20	56	191	509	1,771
Pneumonia								
Monmouthshire	20	54	17	73	94	223	363	339
Glamorgan	24	39	33	55	97	160	333	459
*Western Area	16	15	44	47	137	368	460	228
All occupied and retired males	21	28	40	72	103	170	276	472
Respiratory Tuberculosis								
Monmouthshire	24	87	90	78	67	112	—	—
Glamorgan	58	84	65	106	119	160	194	66
*Western Area	32	201	158	119	254	158	—	—
All occupied and retired males	69	136	133	160	166	150	114	64

* Brecnockshire, Carmarthenshire, Pembrokeshire.

silicosis on the one hand and the silicotic metalliferous miner on the other. The only outstanding difference found by the writer lies in this: that the collier accumulates in his pulmonary tissues a vast store of finely divided coal-dust which is not uniformly distributed but tends to become concentrated under the pleura, especially about the apices, in the interstitial tissue between the lobules, in the perivascular and peribronchial lymph channels and in the lymph nodes at the roots of the lungs and in the mediastinum. It is known that coal-dust is one of those dusts which are most easily removed from the healthy lung by the normal machinery of

alveolar phagocytosis and intracellular transport along the patent and unobstructed lymph-channels. Its accumulation in the silicotic lung is the expression of a profound interference with the drainage system brought about by the inhalation of a silicious dust. The resultant accumulation of coal-dust may assume remarkable proportions; as may be seen from table 2 of the paper by Cummins and Sladden (1930) dealing with this side of the question; and in which it is shown that up to and over 100 gm. of coaly material were in some cases found to be held in the pulmonary tissue.

It is a matter of great interest that this vast accumulation of an adsorbent material, known to possess marked powers of removing toxins from solutions, should coincide with the curious freedom of the silicotic collier from "phthisis." Among the colliers themselves, the antitoxic properties of coal dust are recognized in the remarkable exemption of cuts and scratches impregnated with coal dust from suppuration. It is a common thing to find the skin of a miner "tattooed" from some old accident involving deep excoriation of the surface and simultaneous impregnation with coal-dust; such injuries tend to heal in a rapid and satisfactory manner. It is not to be supposed that no germs gained access to the skin, any more than it is to be supposed that the anthracotic lung is spared from the arrival of inhaled tubercle bacilli during the domestic and social life of the miner; but the presence of germs seems to be tolerated with an unusual kind of indifference, as if the toxic part of the process of bacterial invasion were, in some way, cut out. Experiments by the writer and Dr. Weatherall (1931) have convinced us that coal-dust is able to adsorb a considerable amount of the active element of tuberculin, and we have ventured the suggestion that the accumulation of coal-dust in the lungs of silicoanthracotic colliers may have the effect of detoxicating the tuberculous foci which must arise in a silicotic lung from time to time. Certain it is that much of the "bronchitis" of old coal-miners is complicated by the coexistence of a tuberculous element of a type relatively so benign that it usually escapes notice and only comes to light in the course of some special investigation such as that recently carried out by Enid Williams in South Wales.

SUMMARY

Much is known about silicosis but a great deal of unconfirmed guesswork has accumulated around the known facts, and further systematic research is needed.

We know that "silicosis" is a state of bilateral lung and gland fibrosis, for the most part nodular in type, resulting from the inhalation and the retention in the lung of the dust of hard stone; the particles being in such fine division as to enter the pulmonary alveoli and ultimately the lung tissue, where they set up characteristic changes and determine an increased liability to pulmonary tuberculosis. We know, too, from the animal experiments of reliable investigators, that free silica introduced into the tissues, either in its crystalline form or as a sol, sets up inflammatory processes leading on to fibrosis; and that its presence acts as an adjuvant to the local multiplication of tubercle bacilli.

In the light of this knowledge, the industrial hazard of metalliferous mining and other work on rock containing a high percentage of free silica is regarded as due to exposure for a sufficient time to a harmful concentration of silicious dust and to the associated risk of tuberculosis.

Economic importance is lent to these facts by the necessity to award compensation for the disabilities produced; and this has led not only to intensive study of silicosis and its complications but also to the formulation of definitions based not on scientific knowledge alone but also on legal convenience. Some of these definitions tend to impede rather than to facilitate the elucidation of the silicosis problem.

Recent observations prove the occurrence, in South Wales coal-miners, of a condition corresponding to the silicosis of metalliferous miners in its clinical, radiological and histopathological characters, but apparently free from augmented liability to fatal lung tuberculosis.

These observations raise new problems as to the biological implications of previous work on silicosis and as to the validity of the criteria on which a diagnosis of silicosis is usually made.

The highly organized work of the Miners' Phthisis Bureau of South Africa has provided so much accurate information about the silicosis of gold-miners on the Rand that we are, perhaps, in danger of applying too confidently the Johannesburg findings to allied problems elsewhere. Even on the Rand, the dust inhaled by underground workers contains other elements than free silica; and this is still more true of the mixture of coal-dust and various stone dusts inhaled by colliery workers in South Wales. Some of the elements of these complex dusts may be adjuvants to the action of free silica; others may tend to neutralize it. Indeed, some of the pathogenic effects attributed to free silica may, in reality, depend on associated mineral constituents. The recent work of Badham in Australia on the effects of silicates and that of Dr. W. R. Jones at the

Royal School of Mines, London, on the presence of finely divided sericite, both in the lung residues of silicotic colliers and in the rocks of the South Wales coal measures, deserve close attention; especially as this substance is also a constituent of the Johannesburg banket and was included by Watkins-Pitchford and J. Moir as an important element among the doubly refracting particles in silicotic lungs. The adsorption properties of coal-dust for toxic substances including some of the constituents of tubercle bacilli also call for further study.

It is time that we admitted serious lacunae in our knowledge about silicosis. We need a scientific "recessional" in which to reëxamine with an open mind many of the generalizations now accepted as current coin in relation to silicosis and "Miners' phthisis."

CONCLUSIONS

1. Both in gold-miners and in coal-miners there is a long-drawn-out phase of pneumonoconiosis during which the gradually increasing lung fibrosis and lymph stasis still remains below the "clinical threshold" and the individual continues able to work.

2. This state of "pneumonoconiosis consistent with health" slowly gives place to a phase in which dyspnoea becomes increasingly prominent. This "miner's dyspnoea" represents a stage of definite physical debility which, though not an immediate menace to life, is to be regarded as interfering with wage-earning capacity and as involving a definite risk of serious complications.

3. In metalliferous miners, the phase of "miner's dyspnoea" is markedly liable to pass on into active tuberculosis accompanied by wasting and toxicity; a condition best described as "miner's phthisis."

4. In colliers, "miner's dyspnoea" shows, on the whole, but little tendency to develop into "miner's phthisis," in spite of the fact that tuberculous infection has been proved to be common among them. The dyspnoeic phase often increases in intensity with advancing years and is associated with a high mortality attributed to "bronchitis" in old age. Both the increasing tendency to dyspnoea and the relative exemption from the toxic type of tuberculous "phthisis" are attributable to the accumulation of coal dust in the silicotic lung.

5. Our knowledge of the aetiology of pneumonoconiosis is still too imperfect to justify any sharp differentiation between "silicosis" and "silicatosis." The condition known to-day as "silicosis" may yet be found to be due, in whole or in part, to a silicate. Further experimental work with pure mineral dusts is needed to clear up this point.

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THE CLINICAL ASPECTS OF SIMPLE SILICOSIS AND SILICOSIS WITH TUBERCULOSIS[1]

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Silicosis, at least the most important of the pneumonoconioses, occupies a unique position among pathological pulmonary states which are characterized by abnormal fibrous-tissue formation. The various steps in the evolution of knowledge concerning silicosis are of very considerable historical interest but cannot be recounted here. It is sufficient to recall that our present degree of knowledge regarding this became possible only after the roentgen-ray was applied in photography of the chest.

Although many pathologists doubt whether the fibrosis of the lung which constitutes the essential pathological nature of silicosis ever arises independently of a primary infectious process, it is conceded that the lung tissue must be invaded by finely divided particulate matter in the form of dust, in order that this type of fibrosis may occur, and that the dusts responsible usually contain silica and are almost exclusively of occupational origin.

Clinically, if not from a pathological point of view, forms of the condition do occur in which it is impossible to demonstrate by clinical means an infectious element. Such forms have been termed, in accordance with the custom of the South African observers, *simple silicosis* (1).

Simple silicosis is the form in which silicosis is most commonly encountered in routine examinations of individuals exposed to dust inhalation. It is probably the least commonly seen in ordinary clinical practice, because pulmonary tuberculosis so readily complicates simple silicosis that silicotic fibrosis rarely reaches advanced stages without its occurrence. When this complication is present it is no longer simple silicosis. Further, unless the fibrosis is advanced, simple silicosis seldom occasions conscious disability of sufficient severity to impel affected individuals voluntarily to seek medical advice.

The development of silicosis in the individual patient depends to a con-

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siderable extent on the intensity and duration of his exposure to dangerous dusts. It is therefore found to develop more readily in persons engaged in certain occupations. Variations in this respect are found also in the different units of similar trades, dependent on the differences in efficiency of the measures in force for the abatement of dust. As a rule the sand-blaster and the operator of a natural grindstone have a relatively short working life, whereas that of the moulder or granite-cutter is of fair duration. In practice much indiviual variation in occurrence and progression is encountered. This is customarily explained on the grounds of individual resistance. It would appear, nevertheless, that in silicosis whatever resistance obtains is relative and that no exposed worker is immune. All may acquire the condition if sufficiently exposed.

Individuals inhaling dust often develop a hacking cough early in their exposure. This is sometimes referred to erroneously as an early symptom of silicosis. However, it has necessarily nothing to do with its development. This early cough indicates respiratory irritation and clears readily when exposure is discontinued. The onset of a simple silicosis is, as a rule, gradual. The first and most important symptom is shortness of breath on slight exertion. Dyspnoea varies from slight to extreme, depending on the degree of involvement. This may be the only complaint, but it is accompanied frequently by that of chest pain, cough (more common in the morning) with more or less sputum which may at times be blood-stained. Occasionally small haemorrhages occur. In simple silicosis the general condition tends to be good. Poor general condition, and such symptoms as fatigue, loss of appetite and decline in weight are always suggestive of an accompanying tuberculosis.

Clinical signs in silicosis are for the most part those common to fibrosing lung conditions. They are therefore not characteristic except that they generally occur throughout the chest and are not confined to circumscribed areas. An alteration of considerable diagnostic value, however, is very often observed in the character of the breath-sounds. This consists of a lessening in their intensity or blanketing together, with a shortening of the inspiratory phase, which is at the same time raised in pitch. The shadows to be seen in the skiagraph, when considered in conjunction with a clear history of exposure, are diagnostic. These distinctive shadows are so important that they merit description in some detail.

Before describing these skiagraphic appearances let me recall briefly the underlying pathological process which occasions them. You will remember that silicosis is distinguished by a widespread formation of

fibrous tissue which assumes a nodular or islet formation. These characteristic nodules first make their appearance in relation to the points of division of the bronchial tree and later develop throughout the lung. After having made their appearance they tend to enlarge by peripheral extension, and may run together or coalesce to enclose considerable areas of lung tissue. It is these dense fibrous islets throughout the lung which produce in the chest skiagraph the distinctive shadowing termed *mottling*.

The appearance of mottling is preceded, as a rule, by a change in the general lung shadows which, although observed in X-ray photographs of exposed individuals, is seen also so frequently in unexposed individuals that it cannot be considered a diagnostic sign. This nonspecific change consists of an increase in the hila and an exaggeration of the normal linear shadows. When true silicosis is present, beading of these exaggerated linear markings is observed, particularly related to the points where they show division. This beading enlarges and ultimately assumes the appearance of mottling. When the mottling is well established it detaches itself from the linear shadows which then tend to decrease.

The mottling of silicosis observed more or less throughout the lung-field is almost pathognomonic. It varies somewhat in character and regularity, depending, it would seem, on the type of exposure responsible for the pathological process which occasioned it. The individual shadows are more or less rounded. They are rather soft in texture or of mild brilliancy. Intensely brilliant mottling is not characteristic. It suggests a tuberculous process rather than silicosis. The outline of the nodular shadow is seldom sharply defined. It may be quite irregular. When surrounded by a haze a complicating tuberculosis may be suspected. Silicotic mottling may be intense or sparse and its individual shadows vary greatly in size. It is first noticed often, as Pancoast (2) has observed, in the midzones of the lung field around the root. Often, but not invariably, it is more intense on the right side. Silicotic mottling usually develops gradually, but sometimes it appears with surprising suddenness.

As silicosis develops in its simple form it is at first rarely associated with any marked degree of demonstrable disability. It may be discovered originally by routine examination of exposed individuals. Involvement, as disclosed by the X-ray film, is usually extensive before any serious disablement can be demonstrated. In silicosis no cure is to be expected. Arrest of the extending fibrosis is all that can be hoped for. The only effective treatment is removal from exposure, a course which in most

instances means the discontinuance of occupation on the part of the individual. Moreover, this serious step is frequently without result, as many cases show extension going on for years after exposure has stopped. Therefore it would seem advisable, unless disability is extreme, to consider this procedure only in the younger age-groups.

In extreme cases removal from exposure is necessary. Sometimes this results in a marked improvement in symptoms. Occasionally cases totally disabled, with grave dyspnoea, have been able to return to light work after a period of complete rest. This improvement in symptoms is not accompanied by any decrease in the degree of fibrosis. In only one instance in our experience has an apparent decrease in fibrosis been observed.

Although simple silicosis may not be initially associated with demonstrable disability, as fibrosis increases disability develops and may become extreme. It may even preclude the sufferer from competing in the labor market. Occasionally simple silicosis results in death.

If demonstrable disability is not often an outstanding feature in simple silicosis, potential disability is always present and should be borne in mind. Silicotics are always poor risks when exposed to intercurrent infection, which in them is apt to produce serious results. Pneumonia is usually fatal. Particularly dangerous is infection by the *Bacillus tuberculosis*.

Tuberculosis is the commonest and most important complication in silicosis and is responsible for the majority of deaths among silicotics. The advent of this disease so alters the clinical picture that complicated silicosis is frequently regarded as a clinical entity apart from simple silicosis. It appears to be considered as such by the South African workers (3), who recognize it as presenting two types which they have designated *tuberculosilicosis* and *silicotuberculosis*.

It is characteristic of simple silicosis that it tends to become complicated by pulmonary tuberculosis. This complication results either from the reactivation of a latent tuberculous focus which predated the development of silicosis or from superadded infection. The change may occur in a silicotic at any time. It may appear immediately or only declare itself after a period of years. It is always suggested by abnormal severity or any rapid increase in symptoms and is accompanied by signs of failing health. Cases of this kind, in which a tuberuclous process appears grafted on a preëxisting silicosis, or those in which tuberculosis develops coincidently with a frank silicosis are termed *tuberculosilicosis*.

The clinical picture in silicotuberculosis is somewhat different from that of tuberculosilicosis. In it tuberculosis is the disease which in point of time first makes its appearance. The tuberculosis dominates the picture and a diagnosis of that condition in the simple form is usually made. In these cases, however, the specific signs of silicosis develop after the tuberculosis is well established. This generally occurs within a few months. Recognition of this form of silicosis is of paramount importance, as this combination represents silicosis in its most serious and fatal form.

The diagnosis of a complicating tuberculosis is often difficult and may require a period of observation. Occasionally this will have to be protracted. With this end in view it is often better to hospitalize patients for a short period, preferably in an institution in which the peculiarities presented by silicosis are appreciated. Any method which may clarify the diagnosis either by ruling out or confirming the presence of the complicating factor should be applied.

In many cases great assistance in diagnosis is afforded by serial chest skiagraphs. In these, changes in the type of shadowing are frequently observed when tuberculosis is present. The changes consist primarily in the appearance of conglomerate areas among the shadows of the silicotic mottling. More often these areas of conglomeration are observed toward the apex, but they may be seen anywhere in the lung fields and are common toward the bases. In silicosis special importance should attach to the development of flare-like shadows extending outward from the hila. Unfortunately chest skiagraphs are often misleading, as shadows of tuberculous origin are frequently masked by those of preëxisting silicosis. Therefore tuberculous involvement may be extensive and be overlooked if undue reliance is placed on the X-ray. Conglomerate and massive shadows, although usually of tuberculous origin, are not invariably so. The lungs of a number of our cases whose chest skiagraphs presented such shadows were at autopsy found to be without tuberculosis. It will therefore be appreciated that complete physical examination is essential. Râles are of importance. Those situated below the upper third of the chest are of relatively great importance in silicosis, because tuberculosis in silicotics is common about the hila and at the bases. Observation should be made of the general condition and frequent weight records are necessary. In all cases frequent sputum analyses should be made. These analyses should include cultures and guinea-pig inoculations. When the sputum is positive it is of the greatest value, but little reliance should be placed on negative results. The lungs of many silicotics whose

sputum had been consistently negative during life have shown at autopsy extensive tuberculous involvement.

The importance of tuberculosis as a complicating factor in silicosis should be recognized. It constitutes the main medical problem encountered among those liable to its development. Attention was in fact first focused on industries carrying a silica hazard by the observation that tuberculosis was rife among workers engaged in them. These observations have since been substantiated by numerous individual surveys and the study of statistical death-tab. It is doubtful, however, whether the peculiar relation which exists between silica in the tissues and tuberculous infection is yet appreciated even by industrial physicians, notwithstanding the light which such workers as Gardner (4) in America and Guy and Kettle (5) in England have shed on the problem by their experimental studies. It is certain that this relationship is not appreciated by the medical profession at large.

It may well be that the tuberculosis arising among those engaged in silica trades plays an important rôle in the incidence and spread of civilian tuberculosis. This possible source of infection has not received the attention it merits as the tuberculosis of silicotics is not considered infectious. This belief has been repeatedly emphasized in the literature. In our experience such an opinion cannot be universally entertained. We have found on investigation as great an amount of infection among the wives and children of tuberculous silicotics as was disclosed in those in contact with ordinary tuberculosis. These silicotic contacts, moreover, showed a somewhat greater occurrence of actual disease than did other groups. This comparison was made between groups examined in the same district. In addition almost invariably the evidence pointed to the silicotic father as the source of infection. In some cases the presence of infection and disease in the children was the means by which a suspected tuberculosis was confirmed in the father. In fatal cases this presence of tuberculosis was substantiated at autopsy.

Let me in conclusion emphasize:

That silicosis is relatively common. It can with a degree of accuracy be distinguished from other conditions, but differentiation between types is frequently difficult.

Tuberculosis constitutes the main problem in silicosis and very frequently makes its appearance in areas other than the apex. Latent silicosis is apt to be present in tuberculous individuals exposed to silica.

These should receive a period of observation before being finally disposed of.

The tuberculosis of silicotics is as infectious as that not associated with silicosis and may constitute a source of spread to the general population.

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ROENTGENOLOGICAL ASPECTS OF SIMPLE SILICOSIS AND SILICOTUBERCULOSIS[1, 2]

HENRY K. PANCOAST AND EUGENE P. PENDERGRASS

Silicosis is receiving increasing recognition as an occupational disease. In the United States this is being brought about mainly in an unusual way and especially at the present time. It is not generally a compensatable disease as is the case in many other countries, and civil legal proceedings instituted by claimants for silicosis or alleged silicosis are increasing in frequency, as was the prediction of many of us several years ago. This is one of the most important factors in bringing the dust hazard strikingly before the attention of insurance companies and employers. While the injurious effects of certain dust inhalations have been known to some of the latter group to a greater or less extent for a long time, employers in general have not fully understood the situation and have been largely ignorant of means of combating the hazard. Truly the wheels of progress have been slow in the latter respect.

Only a few years ago, one of us had occasion to visit a small granite-cutting establishment. On looking around the yard and buildings it was noted that the pneumatic-tool men were inhaling considerable quantities of dust that was obviously of a dangerous character. A question to the manager as to the frequency of pulmonary disease among the employees brought forth the answer that a great many of them succumbed eventually to "the rot," but that no preventive measures were known. It would seem that the responsibility for such a state of affairs might rest more upon the shoulders of the medical profession and public-health boards than upon the employers of labor, who, because of their utter lack of medical or industrial hygienic knowledge, must of necessity be ignorant of means of protection. If silicosis and certain other forms of pneumonoconiosis are in a large measure necessary hazards in commercial developments attendant upon the progress of civilization, it should have been among the duties of the medical profession, state health boards and

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[2] Read at a joint session of the Clinical and Pathological Sections at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 29, 1933.

students of the physical problems of dust elimination to fully acquaint industry with much-needed knowledge, and of state legislatures to enact protective regulations. Even now the whole subject remains very much in a state of chaos. Education of all employers as to dust hazards and their control and of governmental regulations is very essential.

The majority of medical students still graduate and enter the practice of medicine with almost no knowledge of the condition of *silicosis*. They learn much about pulmonary tuberculosis and the various factors which predispose the individual to the incidence and progression of this specific infection, and yet silicosis is very often forgotten in this category in their instruction. One of the worst features of silicosis is the predisposition it may afford to the contracting of certain respiratory-tract infections, especially tuberculosis. The workers in any dusty industry are entitled to the same incidence of tuberculosis as is the remainder of the civil population in the vicinity. Unhygienic surroundings under working and living conditions may add somewhat to the incidence of this infection. When a dusty atmosphere associated with industrial employment is productive of definite silicosis, and the incidence of tuberculosis is considerably and obviously increased thereby, the silicosis comes under suspicion as a predisposing factor in the infectious process. This does not mean that every case of tuberculosis in the industry or even every case of silicosis has its infection brought about either primarily or secondarily through the agency of the dust, because some of the employees in a large industry would develop tuberculosis anyway. We must be careful not to jump at unwarranted conclusions in regard to the relations of the two conditions.

The roentgenological examination is the most exact means at our command of determining the presence of pneumonoconiosis, the degree of progression and the differential diagnosis from other conditions. It is equally exact in the detection of uncomplicated tuberculous processes in the lungs. The differentiation between pneumonoconiosis and tuberculosis and the determination of both conditions as coexistent is not always so simple a matter, however, and may be well-nigh impossible, at least without a wide experience based upon the essential factors in the special training required. Roentgenologists must be most careful in their technique. While a large percentage of silicotic cases present spectacular and characteristic appearances in the roentgenograms of their chests, there are very numerous pitfalls for the roentgenologist who has not had the proper training and experience.

It has seemed advantageous to discuss the relations of tuberculosis and silicosis under certain definite groups of cases which will be dealt with in numerical order as follows:

1: The first group to be discussed comprises those cases of pulmonary tuberculosis in which there can be found no roentgenological evidences of silicosis after several years of service in a dust-laden atmosphere, and the condition present is obviously only tuberculosis. We must bear in mind that dust exposure does not preclude the possibility of anyone contracting tuberculosis. The discussion of this group must include the differentiation of the evidences of the infection from all of the phases of pneumonoconiosis,—the perivascular-peribronchial-lymph-node, the nodular, the interstitial, and the terminal predominances. We have seen all of these phases interpreted from roentgenograms when tuberculosis was obviously the only condition present. In some of these cases compensation had been granted and in others claimed on the basis of silicosis simply through lack of diagnostic experience and because the claimants worked where the production of a silica-laden atmosphere was assumed as a possibility. The differential diagnosis in this group resolves itself into the ability to recognize evidences of any of the above-mentioned phases of silicosis, on the one hand, and those of pulmonary tuberculosis on the other. There seem to be many roentgenologists who are not able to do this although they make the attempt, and especially in connection with compensation cases. A further discussion of this group would entail a prolonged dissertation on both diseases. It should be borne in mind that this group does not include cases which may have both conditions, but tuberculosis is the only one present.

2: The second group of individuals to be discussed includes those cases of obvious pulmonary tuberculosis in which there are evidences of a very mild degree of silicosis or pneumonoconiosis after several years of service in an industry, but in which it seems reasonable to believe that the latter condition is not a predisposing factor. By the term "mild degree" is implied the perivascular-peribronchial-lymph-node phase, a very moderate nodular appearance or an interstitial phase, any one of which, or all if present together, have been produced or have been found after 10 to 50 years' occupation in the same industry and under approximately the same conditions as to physical factors. In many instances it is easy to draw the line between predisposition and lack of it, but in some cases

this is a very difficult question to settle, and the value of the decision must be governed to a considerable extent by the diagnostician's ability and experience. The law in some countries gives every worker the benefit of the doubt when both conditions are present, and justly so in many instances, and, no doubt, unjustly in others. Unfortunately, animal experimentation is of little or no value in helping us to decide whether a very slowly progressing pneumonoconiosis, requiring many years to become evident in even a minor degree, is in any way a predisposing cause of the infection, because it is impossible to obtain proof of the action of silica or other dusts when inhaled in moderate quantities upon animals over a period of very many years. Ordinarily one recognizes two distinct types of human pulmonary tuberculosis,—childhood and adult,—which are in many respects almost different diseases. Anyone familiar with silicosis must recognize a third type, namely, silicotuberculosis, which presents many points of difference from the other two, and which will be discussed later.

In the group of cases now under discussion we would not use the term *silicotuberculosis*. In these individuals one would expect to find the usual appearances of adult tuberculosis, and throughout its course. In many instances we have noted evidences of a tendency to heal with only the usual amounts of fibrosis. Complete clinical and roentgenological healing of such lesions would almost always imply lack of predisposition by reason of dust. Lack of complete healing may leave one in doubt as to future predisposition and change in type, whether the individual changed his occupation or not, and subsequent serial examinations would have to be the deciding factor. In this connection it should be borne in mind that silicosis may be a progressive condition for many years after cessation of the dusty occupation, and predisposition may become manifest a long time after the dust exposure. An excellent example of this kind was observed in a man first examined in 1924, when his occupation was unknown. A diagnosis of pulmonary tuberculosis of the usual adult type was made. Five years later he was seen again, the appearances had changed to those of silicotuberculosis or diffuse terminal silicosis, and it was then learned that he had been both a miner eighteen months and a fire-brick worker for five or six years, ten years prior to his first visit to us (figures 1 & 2).

Our greatest experience with the group of cases under discussion has been in connection with coal-miners. The frequently alleged protection against tuberculosis afforded by coal-dust is well known to everyone interested in pneumonoconiosis. We have previously referred to the opinions

pro and con (1) (2) (3). In discussing this problem we must not lose sight of the fact that in the coal-miner we are dealing with two different kinds of dust, and, therefore, two entirely different conditions: one, anthracosis, due to coal-dust alone and relatively harmless, and the other, best designated by the term *silicoanthracosis*, recently used by Cooke (4), and due to a mixture of coal-dust and silica. Pure coal-dust by itself, does not produce more than a mild degree of pneumonoconiosis and probably does not in itself, or through its own effects alone, predispose to tuberculosis (figure 3). If tuberculosis occurs in the pure anthracotic it is likely to take the usual form of adult tuberculosis. On the other hand, there seems to be conclusive evidence presented by Cummins (5), Middleton (6), and others, that coal-dust enhances the action of silica when the latter is inhaled in large amounts, but Mavrogordato (7) (8), Heffernan (9), and Heffernan and Green (10), and others believe that when the intake of silica is slight, the action of coal-dust may be a retarding one on the silica. Certainly the excessive inhalation of both dusts is productive of a predisposition to tuberculosis (figure 4). Cooke (4) states that retention of coal-dust to any serious degree does not occur unless the lymphatics of the lung have been previously damaged by the action of silica, in which case the coal-dust is capable of accumulating and leading to serious and even fatal disease.

3: The third group of cases for discussion comprises a very important one in which the individuals present obvious tuberculosis associated with slight evidences of silicosis after a comparatively short period of occupation, and yet it is most likely that the silicosis is a definite predisposing factor in the infection and its progress. There may be another factor of the silica-saturated lung to be considered, which will be discussed later in connection with group 4. This present group has been a very interesting one to us and one which confused us considerably until we became oriented, because it was a new experience. We refer particularly to sand-pulverizers and workers in some other industries, who are exposed to unusually large amounts of dust containing a very high percentage of silica. The stand-pulverizing industry has been referred to in a previous communication (3). In the incapacitated individuals tuberculosis was the striking feature. In most cases of this group the evidences of silicosis were slight and were limited to the rapid interstitial phase, apparently because of the short time of exposure to the surcharged atmosphere before the period of incapacity arrived (figure 5). The tuberculous manifestations were almost invariably those of a diffuse pneumonic process (figures

6 & 7), unlike the cases of more chronic silicotuberculosis. Moreover, the clinical aspects differed. There was a rapid onset of dyspnoea, cough, haemoptysis, night-sweats, asthenia and extreme weakness, in contra-

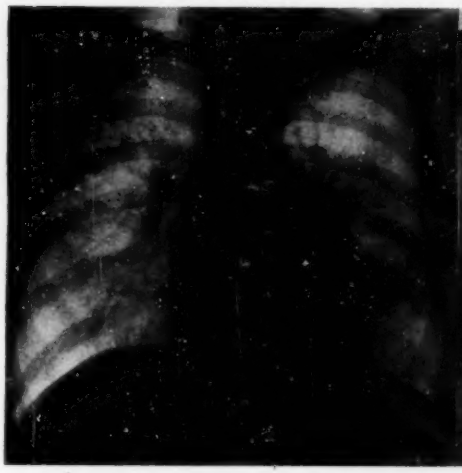

FIG. 1

FIG. 2

FIG. 3

FIG. 4

distinction to the characteristic comparative freedom of the more chronic cases from serious symptoms until near the end. We have no way of determining whether any of those cases had tuberculous lesions before starting work, or whether some or all contracted the disease during their

comparatively short time at their occupation. All of these workers were cases in which a complete knowledge and understanding of the physical

FIG. 1. Male, aged 35 years, examined August 12, 1924, occupations then unknown. Referred with history of recent pneumonia and left pleural effusion. The right upper lobe shows two areas of recent exudative tuberculous process, some intensification of the basal trunk shadows and a diffuse fine mottling of the midlung field, appearing in the reduction as a faint haze. The left lung shows a tuberculous lesion, with cavity in the upper portion of the lower lobe and a mottling in the lower lung field shown in the reduction as a marked haze. There is pleural thickening at the left base. The diagnosis was tuberculosis, but silicosis should have been added had the previous occupations been known.

FIG. 2. The same case as illustrated in fig. 1, November 23, 1929. Examination made because of gradually progressing dyspnoea and signs of left-sided pneumothorax. Both lungs show large consolidated areas and conglomerate nodules at the right base. There is a spontaneous pneumothorax at the left base. The appearances led to questioning as to occupation and it was then learned that the patient had been a miner for eighteen months and a fire-brick worker for five or six years, ten years prior to the first examination. A diagnosis was then made of silicotuberculosis. This case demonstrates the value of serial studies in establishing the presence of both conditions and the predisposition of silicosis in the incidence and progress of tuberculosis. The arrow points to the increased prominence of the pulmonary artery probably due to back pressure from the pulmonary fibrosis.

FIG. 3. This represents what we have regarded as about as advanced a case of pure anthracosis as it is possible for one to find. The man, aged 59 years, worked in a coal-mine for three months, thirty years ago. He next worked in breakers for twenty years. The past ten years have been spent in clerical work. Previous medical history negative except for pleurisy two or three years ago. Wife and daughter died of tuberculosis. Chief complaint, recurring corneal ulcers of unknown aetiology. No cough or chest symptoms and feels perfectly well. Temperature, pulse and respiration normal. Wassermann negative. In the roentgenograms, the lungs show a moderate increase in prominence of the hilum and trunk shadows even for the age. There is no nodulation. The lateral views showed marked emphysema. In each upper lobe there is a rather sharply circumscribed consolidation believed to be due to pneumonoconiosis and mainly anthracosis. These are not at the periphery except in being at the bases of the upper lobes posteriorly as shown by lateral views. There is no tracheal deviation or distortion in either view nor any displacement of either hilum shadow. We would regard these shadows as due to an advanced interstitial phase of anthracosis. By stereoscopic observation one can see a definite thin-walled cavity in the extreme right apex, obviously due to the usual adult forms of tuberculosis, and not such a lesion as one sees in silicotuberculosis.

FIG. 4. Terminal diffuse silicosis with tuberculosis. This man, aged 51 years, had been a coal-miner for thirty years. He was referred from an asthma clinic in another institution. In addition to his incapacity, he had been coughing up considerable sputum, containing a large amount of coal-dust for some time. The roentgenograms show a diffuse massive fibrosis in the midportion of each lung. These may or may not be tuberculous as well as silicotic, but they probably are. There is an obvious tuberculous process in the upper right lung, with a large cavity and drawing of the trachea to the right. This is no doubt silicotuberculosis. The lower lung fields show marked emphysema and some interstitial and nodular phases of pneumonoconiosis which are not reproduceable. (Courtesy of Dr. G. R. Miller.)

factors incident to the industry were absolutely essential in the correct roentgenological interpretations.

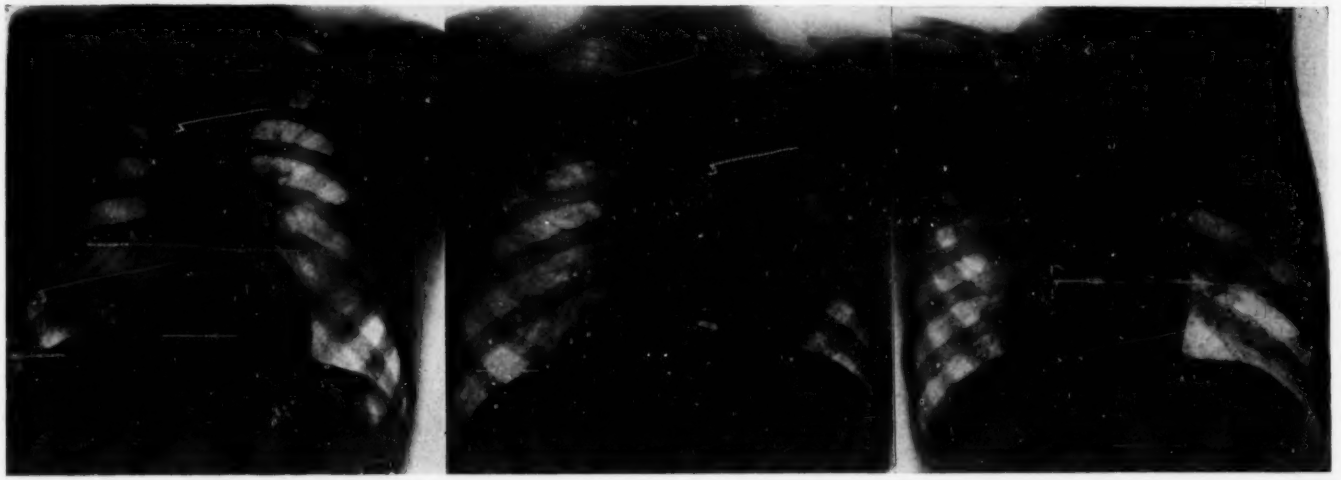

FIG. 5 FIG. 6 FIG. 7

FIG. 5. Rapidly developing silicosis with early interstitial predominance. Male, negro, aged 36 years. He worked in a sand-pulverizing plant for several months. The only significant finding was a general diffuse haze in the lower half of the right lung, with extremely fine mottling seen in the roentgenogram but not reproduceable in this reduction. The same appearance is just beginning in the lower left lung. Diaphragmatic excursion: right dome 13 mm. and left dome 30 mm. The predominance of the interstitial phase of silicosis with greatly restricted diaphragmatic excursion in a short-time worker in a hazardous dust gives a bad prognosis, especially as to the incidence of tuberculosis, which usually assumes a rapidly developing pneumonic form, although in more slowly developing cases one may observe typical silicotuberculosis. In either instance the evidences of silicosis are apt to be very much or entirely obscured. This type of case will not develop a nodular predominance of silicosis.

FIG. 6. Advanced pulmonary tuberculosis in a male negro, aged 27 years, who worked 7½ months in a sand-pulverizing plant. Chief complaint dyspnoea, cough, haemoptysis and weakness. Tuberculosis is the predominant feature and obscures any silicosis that may be present. The normal appearance of the right lower lobe certainly shows no evidence of silicosis although the individual's co-workers had it. This is a good example of the cases discussed under group 4. Did the rapid intake of silica predispose to the infection or cause a rapid spread of one already established before demonstrable evidences of silicosis could occur? This individual died a few months after the examination.

FIG. 7. Right anterior oblique view of the same case illustrated in fig. 6, showing to better advantage the sharp limitation of the peripheral portion of the right-sided process to the upper lobe. Note the lack of involvement of the right lower and middle lobes. This is a very important view in such cases, and illustrates the modifications in technique often required in silicotic suspects for accurate diagnosis.

4: The fourth group, which merits separate consideration, embraces cases of obviously advanced tuberculosis in which there are no demonstrable evidences of silicosis, or, if present, they are entirely masked in individuals working under conditions in which the physical factors in the occupation would lead one to suspect the possibility of a rapidly developing silicosis, as in group 3. The essential theoretical point is that the intake of silica has been unusually rapid, but there has not been sufficient time for demonstrable fibrosis or even demonstrable prefibrotic stages to become established (figures 6 and 7). The question arises as to whether a silica-saturated lung, with the preliminary stages of silicosis in progress, can act as a predisposing factor in the incidence of tuberculosis or can reactivate old but unhealed lesions. We have frequently come in contact with cases in which these questions have arisen and it is an issue we can no longer evade.

These two aspects of the situation must be considered separately, and we will discuss the second one first. It would seem that the question of reactivation would have to be answered largely by the results of animal experimentation. Gardner (11) states that it has been generally assumed by clinical investigators that the terminal tuberculosis, which causes the deaths of at least 25 per cent of silicotic subjects, is the result of infection *acquired* during industrial life. Hence he carried out a series of animal experiments to determine whether or not certain dusts might not *reactivate* old, partly healed foci, and from this source produce endogenous reinfection. Guinea pigs were infected through the air-passages by the author's usual attenuated strain of tubercle bacilli, which produced the typical "primary complex" with definite tendencies to limitation and healing and the usual primary involvement of regional lymph nodes. Groups of infected animals were dusted with quartz, granite and carborundum dusts respectively. The dusting occurred at intervals when the healing process was started, well under way, or nearly completed. We are interested particularly in the effects of quartz dust, containing 99.34 per cent SiO_2. In the first group, when dusting began 54 to 87 days after infection and was continued 8 hours per day, except Sundays, for variable periods, there was a spread of the tuberculous process in all the animals. In those exposed to dust 151 and 177 days after infection, there was evidence of a spread in 60 per cent. In the third group, in which dusting began 206 days after infection, 33 per cent showed spread. This was usually most marked in those animals dusted for the longest period before killing. The spread developed by direct extension from the pri-

mary foci with or without subsequent widespread bronchogenic dissemination.

We are particularly interested in the question as to whether reactivation of tuberculous lesions can occur before it is possible for any demonstrable evidences of silicosis to become apparent. Gardner's experiments would seem to prove *that it can*, but we must bear in mind that his quartz-dusted animals were exposed to an atmosphere containing 859 million particles per cubic foot under 10 micra, of which 188 million were under 1.5 micra in size, which are very high silica dust counts for human industrial exposures. On the other hand, we must remember that the microorganisms in the human subject are of much greater virulence than those used by Gardner.

Let us approach the problem from the standpoint of reactivation during a prefibrotic stage of silicosis. Gardner and many other investigators have shown us, and many of us have seen for ourselves, that dust-cells will phagocyte very variable numbers of particles of different dusts, and that in the case of silica only as few as one to four particles will be incorporated, compared to enormous numbers of coal or carborundum particles. Probably, or at least, mainly for this reason, according to Gardner, quartz gives no limitations to locomotion and rapid removal to lymphoid tissue, nor does it interfere with physiological action in the sense of phagocytosis for the tubercle bacillus. It is also known that a reactivated tubercle has included in its structure great numbers of dust-cells. Gardner states that it is uncertain just how the dust reactivates the quiescent tuberculous focus. It has been proved that inflammatory reactions, specific in the case of the frequent incidence of Friedländer pneumonia, and nonspecific through the applications of irritants, are not the factors *per se*.

Gardner (11) concedes that, in view of our present knowledge, or lack of it, the action must be chemical, either by silica or some other substance. He regards two general views as tenable: (1) that silica may injure the tissues and produce an environment particularly suitable for the growth of the bacillus through the elaboration of some substance by the action of silica on the body-cells and better suited to the microörganism than its environment in the tubercle protected from body-fluids by a wall of hyaline fibrous tissue; and (2) that in dilute solution silica stimulates proliferation of the bacillus, although we have as yet no accurate information as to such solubility in body fluids.

The second aspect of the situation, in regard to the newly silica-satu-

rated lung acting as a predisposing factor in the *incidence* and rapid progression of a tuberulous infection, is not so easily disposed of. The foregoing remarks on animal experimentation would certainly apply to the rapid progression of the infectious process when once it had been initiated. Predisposition under the circumstances imposed has not been proved, but it is an issue which must be met. We are inclined to regard it as a strong possibility as yet unproved. The type of case discussed under group 3 would lead one to suspect the possibility from both clinical and roentgenological standpoints.

As to the roentgenological appearances in such cases, whether the infection was reactivated or incidental through chance or predisposition, we might expect the usual rapid forms of adult tuberculosis or a rapidly progressing and spreading pneumonic process, such as were encountered in many instances in group-3 cases and as illustrated in figures 6 and 7. The important deciding factor in predisposition for the incidence of infection or in the silica saturation being the cause of reactivation and progression cannot be the roentgenological examination, because the latter does not show evidences of silicosis. The decision for the present, at least, must rest almost solely upon the actual and *proved* physical factors present in the individual's occupation, which must be beyond all shadow of doubt before condemning a man to this group or placing the responsibility.

5: The fifth group comprises those cases of obvious tuberculosis in which there is evidence of a rather advanced silicosis which could readily be a predisposing factor in the incidence of the infection. This group embraces a large number of cases, and has received wide recognition. The peculiar feature of this group is that the roentgenological evidences of the infection are usually out of all proportion to the clinical aspect of the cases (figure 12). These cases are well recognized as one of the group of silicotuberculosis. The rapidity of progress of the infection is often, if not usually, commensurate with that of the silicosis. In the more slowly developing cases of silicosis the infection behaves differently from ordinary tuberculosis. As Gardner (12) states, the clinical study of human pneumonoconiosis complicated by tuberculosis has shown that the disease tends to run a chronic course, and the symptoms of intoxication are not so pronounced as in undusted individuals. The slow progress is due to the fibrosis, which is usually intensified by the combination of the two conditions, as is generally recognized. Gardner regards the lymphatic obstruction of the silicosis as sufficient explanation for the lack of toxic symp-

FIG. 8

FIG. 9

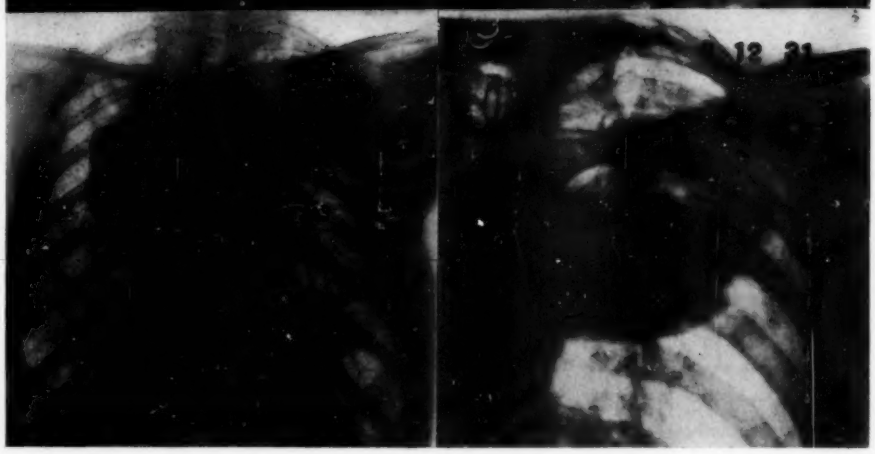

FIG. 10

FIG. 11

FIG. 8. Terminal silicoanthracosis with massive fibrotic areas in a coal-miner 53 years of age and 42 years' occupation. He was well until 18 months ago, when gradually increasing dyspnoea began and obliged him to give up work. Physical examination was negative except for emphysema. The areas of massive fibrosis seem to take origin mainly from an interstitial phase of the condition rather than from conglomerate nodular change. The location of these areas centrally, and well away from the periphery, tends to prove they are silicotic and not tuberculous. There was no tracheal displacement in the roentgenograms.

FIG. 9. Overpenetration of the right upper-lobe lesion of the case illustrated in fig. 8, and use of Potter-Bucky diaphragm, show a finely reticular form of shadow, with the trabeculations close together and not coarse as in tuberculosis, and the absence of cavitation and calcification.

FIG. 10. Silicotuberculosis with massive bilateral shadows in a coal-miner, 66 years of age and 26 years' occupation. He has been unable to work for 8 years because of dyspnoea, pain in the right chest and cough. Has morning expectoration. Roentgenograms show large areas

toms. Obviously the more rapid the progression of the silicosis the more likely is the infectious process to be influenced like the cases of groups 3 and 4.

6: Our sixth group embraces the cases of definitely advanced silicosis, in which there is doubt as to the coexistence of tuberculosis, or it is impossible to identify evidences of the infectious process with any degree of certainty. This group also includes a large number of cases. In reality this and group 5 are much the same and differ mainly in the difficulties which may be encountered in diagnosis. We may recognize three general types of cases in which the diagnosis of an accompanying tuberculous process may present difficulties:

(1) The differentiation between massive fibrotic consolidations of the terminal stage of silicosis from massive tuberculous lesions which are made up of a large amount of fibrosis as a result of the accompanying pneumonoconiosis. Such lesions have the contracting characteristics of any large fibrosing tuberculous areas. They may be bilateral, but the chances then are that one side started before the other or progressed further and fibrosed more than the other. One must regard these lesions as of tuberculous or partly tuberculous origin when they are *peripherally located.* The unilateral or older bilateral lesion of this nature will cause homolateral displacement of the trachea and possibly the vessels, and, because it must retract upward and outward, the hilum shadow is apt to be similarly displaced. These displacements were brought to our attention in the first American paper on the roentgenological aspect of silicosis by Lanza and Childs (13) in 1917. Bilateral purely silicotic consolidations will not displace structures because, first, they are not inclined to retraction, and, second, they are synchronous in their formation. When there are bilateral consolidations, one of which is obviously tuberculous because of the effects of retraction, the lesion on the opposite side may not extend to the

---

of consolidation in both upper lobes. The one on the right is associated with a right-sided deviation of the trachea. The one on the left is lobar and peripheral and the lateral view shows a retracted left upper lobe and marked emphysema. Both areas are suspected of being tuberculous. The stringy appearance of the midlung fields suggests silicoanthracosis, especially on the left, rather than tuberculous spread. The comparative clearness of the bases and regular outline of the diaphragmatic domes indicate that any silicoanthracosis is not advanced.

FIG. 11. Overpenetrated left upper-lobe lesion of the case illustrated in fig. 10, showing coarse trabeculation, cavitation (lower arrow) and calcification (upper arrow), indicating tuberculosis.

periphery and may yet be tuberculous, as indicated by upward displacement of its corresponding hilum shadow. This lack of peripheral location is explained by the fact that it cannot retract upon and displace the central movable structures like the trachea because they have been already fixed by the contralateral lesion. There is still further differentiation to be made by roentgenological studies. If the individual consolidated lesions are intentionally overexposed, especially with the use of the Potter-Bucky diaphragm, considerable difference will be noted in the structures. The silicotuberculous consolidation shadow will appear generally homogeneous, and any stringy appearance due to tuberculous fibrosis will be coarse and far apart, and cavities or calcifications or both may be found. The purely silicotic consolidation will not be nearly so homogeneous and there is apt to be a close trabeculation (figures 8 to 11).

(2) One frequently observes a case in which there is a rather extensive consolidated lesion in the upper chest, more marked on one side or limited to one side. In addition to this there are nodular lesions usually lower down and on one or both sides. This type of case represents a most difficult one for differential diagnosis. If the case is essentially one of tuberculosis, the massive lesion is most likely a rapidly progressive one and the nodular appearance may be due, in part at least, to a bronchopneumonic spread to one or both sides. It would take too long to enter into all of the differential points in such a group of cases, but the one warning that is pertinent is that the differentiation of tuberculosis often requires the maximum of roentgenological diagnostic acuity.

(3) Tuberculous infection may be present in what appears to be a purely nodular type of silicosis. It is far more likely to be a superimposed process, and presumably exogenous in the absence of any typical adult lesion. When the nodules tend to become conglomerate or there is the appearance of considerable interstitial change between them, we may suspect a superimposed tuberculosis, although it cannot be absolutely proved that the appearance is not strictly a transition to a terminal diffuse phase of silicosis. In the typical nodular type, the shadows vary in size from barely visible ones to that of a small pea, and are more or less regular in outline and rather sharply circumscribed, and the density depends considerably upon the size. The question of superimposed tuberculous infection may arise when the shadows are larger and take on a hazy or fuzzy and irregular and much less dense periphery. Gardner's (14) (15) description of the nodule may be very briefly summarized, to the effect that it is composed of a central mass of hyaline tissue surrounded by a capsule-

like periphery of young fibroblasts, which is quite cellular, and with a large number of dust phagocytes interspersed. The nodule becomes larger and macroscopic by subsequent aggregations of cells. Belt (16) states that tuberculous caseation always takes place in the pulmonic areas which remain air-containing, whereas completely fibrosed patches invariably escape necrosis. He often found fibrous nodules completely surrounded by the tuberculous process. The points most vulnerable were the "silica nests," where unaltered silica was collected in large amounts

FIG. 12. Silicotuberculosis in an iron-miner, aged 47 years and 28 years' occupation. Both lungs show perivascular-peribronchial-lymph-node and marked nodular phases of silicosis. In the upper right lung there is a massive lesion, which is obviously tuberculous because of its peripheral location, drawing of the right hilum to the right and upward, and probable cavitation. In the left lung the nodules grow larger and more numerous toward the apex, suggesting that the upper ones at least are the seat of perinodular tuberculous invasion rather than due to silicosis alone. Some of them might be the result of bronchogenic spread of tuberculosis, but they are in a higher location than is usual for this. *This man feels perfectly well.*

in avascular areas around completely fibrosed necrotic lesions of silicosis and where further tissue reaction was impossible. Thus it will be seen, from these two points of view, that the central portion of the silicotic nodule is fibrotic and the outer portion is cellular and active and may be roentgenographically less dense or sharply defined. If the less dense periphery is spreading rapidly under serial studies one may *suspect* superimposed tuberculosis of the perinodular type, especially if this is occurring in some nodules and not in others (figure 12). To make this distinction

by a single examination is likely to be guess-work. Even serial observations must be made by the use of exactly identical technique.

7: Our seventh group includes cases of obvious tuberculosis appearing late in individuals with progressive and marked silicosis which has become evident, or there has been reason to examine for and detect it, many years after the cessation of hazardous dusty occupations, and the individuals have been apparently perfectly well for a long interval. This is a very common type of case which has been profusely dealt with in the literature, and which all of us who have seen many cases of silicosis can recall very readily (figures 1 & 2). It is the type of case which makes a good example for warning employers of labor to use great care in the selection of workers they are about to employ, and to search carefully into the history of past employment throughout the entire period of the worker's previous labor activities.

8: The eighth discussion does not so much concern a definite group of silicotuberculous individuals as it does a pathological problem. Frequently, when examining silicotic suspects, we encounter cases whose roentgenograms show very obvious calcifications in the pulmonary lymph nodes, with or without a calcified primary nodule, and the question arises as to the possible effects of childhood tuberculosis upon the progression of silicosis. In 1925 Gardner (12) stated that the lungs of individuals whose pulmonary lymph nodes were involved with healing or healed tuberculosis would more readily react to smaller amounts of dust and an obstructive fibrosis would occur in a shorter time. He intimated that this might account for the great irregularity in the time required for the development of demonstrable silicosis in industry. We believe this still remains a theoretical problem.

9: The ninth or final discussion bears on the great necessity for care as to the hygienic surroundings in both working- and living-quarters of individuals exposed to silica and other possible harmful dusts. Tuberculosis is a very frequent complication of silicosis, and, as such, is almost certain to be the eventual cause of disability and is quite likely to be the essential cause of death. For both of these eventualities the employer is likely to become the recipient of blame. It is to his interest, therefore, to see to it that hygienic surroundings under living as well as working conditions are kept under observation, because it is highly important that the

worker in hazardous dusts does not contract tuberculosis from an outside source if it can be prevented. Naturally the individual with tuberculosis should not be employed, and, with past evidences of an infection, employment should be considered with the utmost caution. Hot, humid, damp mines with tubercle bacilli and other organisms possibly present are not the most hygienic places in which to work, and adequate ventilation is highly essential. But the miner, or any dusty worker, spends the greater part of his time away from work, and during that part of his life good hygiene may or can be carried out or enforced. In this connection we always have had the greatest respect for the conclusions of Wainwright and Nichols (17) nearly thirty years ago, in regard to the alleged protective influence of coal-mining against tuberculosis. They concluded that the important contributing factors in keeping the tuberculosis rate at a comparatively low figure were the following: The absence of crowding at work; lack of extreme overcrowding in housing; the custom of these miners to walk or ride considerable distances; the compulsory daily bath for obvious reasons; the moisture in the mines preventing sputum from drying and the gradual bacterial purification of the air from mine entrances to the work-chambers. This aspect of industry is certainly a public-health problem and as worthy of regulation as is the dust hazard itself.

SUMMARY

Superimposed tuberculosis is a most important factor in the incapacity and mortality resulting from silicosis and other industrial forms of pneumonoconiosis. The usual clinical manifestations of tuberculosis are often characteristically lacking. The roentgenological study is the most dependable means of diagnosis under such circumstances. This is considered under the following groups of cases:

1. Tuberculosis without roentgenological evidences of pneumonoconiosis after several years of dusty occupation.

2. Tuberculosis with evidences of a very mild degree of pneumonoconiosis after many years of service.

3. Tuberculosis associated with slight evidences of silicosis after very short periods of occupation in very dusty atmospheres.

4. Advanced tuberculosis with no demonstrable evidences of silicosis after work for a short time in extremely hazardous dusty atmospheres. The question of predisposition arises in these cases.

5. Advanced tuberculosis associated with advanced silicosis which could be a predisposing factor.

6. Advanced silicosis with coexisting tuberculosis, but the differentiation of the latter condition is difficult or impossible.

7. Tuberculosis appearing many years after cessation of a dusty occupation, and discovered to coexist with a late-appearing silicosis.

8. The problem of modification of silicosis by an evident preëxisting but healed childhood infection.

9. The necessity for hygienic efforts directed toward the prevention of tuberculous infection among workers is discussed.

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THE OCCUPATIONAL HISTORY AND HOW TO MAKE IT[1]

R. R. SAYERS[2]

The purpose of an occupational history is to try to determine the relation of an individual's physical condition to his work. In many industries this relationship is either without significance or undetermined. In silicosis a relationship of occupation to the physical condition of the worker is well established. A detailed statement on occupation is one of the most, if not the most, important single item in the history of men suspected to have silicosis. A statement that a man is a miner or foundryman or a stone-worker is of little value, as the particular mine or industry may produce no siliceous dust and therefore have no silicosis hazard; further, many occupations in industries having a silicosis hazard produce very little dust, especially when the industry is well operated.

A few years ago the usual form for physical examinations had one or two lines allocated to the occupation, even when these forms were especially prepared for use in industry. In one form, prepared about 1920, the question was: "What is your present occupation?" In another form prepared about the same date but intended for use in industries, two lines were assigned for the following information: "Previous occupations," with instructions to "give principal occupation and length of time engaged therein;" "present occupation," with instructions to "give first broad classification; give any specific designation or duties and describe briefly."

While the makers of this form knew the type of information needed in locating a health hazard, and of use in making a diagnosis, they failed to provide sufficient space to adequately record it.

A third form prepared about a year later, for the study of tuberculosis in dusty trades, was somewhat more detailed. Under the general heading "Trade life" ten lines were provided for recording data under the subheadings: (1) Firm or place of work; (2) kind of stone work; (3) exact oc-

[1] Presented at a joint session of the Clinical and Pathological Sections at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 29, 1933.

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cupation; (4) years followed; (5) former occupation. Almost one-half of the total space was allotted to the last heading.

In addition to the above, fourteen lines were provided for recording the data on dust exposure, under the following headings: (1) Type of pneumatic tools used; (2) how many years; (3) what particular operation is most dust-producing; (4) is general dust exposure apparently harmful?

This form provides sufficient space for recording most of the information obtained; however, it emphasizes the individual's opinion of his own working environment and possibly indicates the preconceived opinion, probably correct in this case, of the maker of the form, and thus may bias the judgment of the investigator.

A fourth form, under the general heading "Occupation," provides a short space on a line to record the data obtained regarding each of the subheadings: (1) Present; (2) former; (3) stopped work. Another line is allocated to the headings: (1) Underground—number of years; (2) surface —number of years. Twenty-four occupations in the industry for which the form was made were each allocated half a line to record the time spent in that particular work.

This form is probably satisfactory for an industry with a practically unchanging personnel, for example, a mine in an isolated community. However, for the average industry located in a large centre, I am of the opinion that it does not contain enough information regarding former occupations of the individuals examined.

In the form used by the U. S. Bureau of Mines, nine lines were provided for the occupational history, under the headings: (1) Total years in mines; (2) hard rock in specified mine, total years; (3) time worked in coal —total years; (4) other mines and quarries—total years; (5) present exact occupation; (6) past exact occupation; (7) years in each occupation. This form, while providing sufficient space to record the data secured, is somewhat confusing without detailed instructions as to the information desired. Further, the form presupposes a job analysis and that the physician making the history is familiar with the detail of the various jobs in the industry.

In the study in which this form was used, a survey of the working conditions was made, with special reference to dustiness, by a physician and an engineer. After the survey was completed, each job was defined or described about as follows: *Shoveler:* Shovelers are men who shovel the ore into cans at the face; they are hired on a contract basis. A can is a

large steel bucket which holds about 1,000 pounds of ore. *Hookers:* A hooker is a man who hooks the hoisting rope to the filled can in the bottom of the shaft.

OCCUPATIONAL AND PAST MEDICAL RECORD

NAME..... NO..... PRES. AGE..... MINE..... DATE.....

AGE BEGAN WORK..... NO. YRS WORKED..... COUNTRY BIRTH..... RACE.....

	OCCUPATION	INDUSTRY	NO. YRS. IN HARD COAL MINES	NO. YRS. IN OTHER DUSTY	NO. YRS. IN NON-DUSTY	REMARKS
PRES.						
PREV: 1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

PAST MEDICAL (INSERT DATE OF ILLNESS IF POSITIVE HISTORY IS RECORDED).

T. B. CONTACT (F OR P)..... WHEN.....
T. B..... INFLUENZA..... SYPHILIS .....
TYPHOID FEVER..... FREQ. COLDS..... SCARLET FEVER .....
PNEUMONIA..... BRONCHITIS.....
PLEURISY..... CHR. RHEUM.....
OPERATIONS .....

PRESENT CHRONIC ILLNESS OR COMPLAINTS (INSERT DATE OF ONSET WHEN POSITIVE)

FREQ. COUGH..... PRODUCTIVE..... CHAR. OF SPUTUM.....
NIGHT SWEATS..... WEAKNESS..... DYSPNOEA .....
PAIN..... LOCATION..... MINERS' ASTHMA.....
OTHER COMPLAINTS .....

OCCUPAT. RECORD TAKEN BY.....
PAST MED. RECORD TAKEN BY.....

These definitions contain a number of words which would need to be explained for the person unfamiliar with the industry; however, when these descriptions were correlated with the industrial-dust survey and the

that some people called "Well" should be in the "Chronic" class, and *vice versa*.

The classification, used in 1929 of the types of blood-picture in known tuberculous individuals, with their meanings given briefly, is as follows:

1: Normal: The total count and each of the cell-types are within certain normal limits. (Total cells, 6,000 to 9,000; neutrophiles, less than 65 per cent, or 5,000 cells; monocytes, less than 10 per cent, or 700 cells; lymphocytes, more than 25 per cent, or 2,000 cells.) It denotes a lack of pathological activity in the lesion, a controlled condition.

TABLE 1

1933		1. WELL		2. WELL AFTER RELAPSE		3. CHRONIC		4. DEAD			5. LIVING AND UNREPORTED	SURGICAL SUMMARY			
												Well	Ill	Dead	Total
Number of cases	250	167 (66.8%)		15 (6%)		37 (14.8%)		22 (8.8%)			9 (3.6%)	38	15	2	55
1929		Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nontuberculous					
Number of counts		134	33	10	5	22	15	18	2	2					
Normal (19%)	48	34	4	0	2	2	1	0	1	1	3	6	1	1	8
Hyperplastic (22%)	55	34	4	4	1	4	4	1	1	0	2	5	4	1	10
Septic (59%)	147	66	25	6	2	16	10	17	0	1	4	27	10	0	37
Resistant:															
With normal	21	15	2	0	1	1	0	0	0	1	1	3	0	0	3
With hyperplastic	18	10	2	3	1	0	1	0	1	0	0	3	1	0	4
Total	39	25	4	3	2	1	1	0	1	1	1	6	1	0	7

2: Hyperplastic: An increase in the mononuclear leucocytes above normal numbers (more than 9 per cent, or 700 cells). The total count, lymphocytes, and neutrophiles are of normal numbers. It denotes new tubercle-formation. A fairly passive type of reaction, both clinically and pathologically.

3: Septic: Primarily an increase of the neutrophiles (more than 65 per cent, or 5,000 cells). There is often an increase of the total count (more than 9,000 cells), and monocytes (more than 9 per cent, or 700 cells), with a lymphopoenia (less than 25 per cent, or 2,000 cells). It denotes tuberculous abscess-formation in some degree and is the most serious type of count, associated with all of the

more active features of the disease. The level of septicity is, in general, an indicator of the magnitude of the disease process.

A lymphocytosis (more than 32 per cent) added to a Normal or Hyperplastic count was seen in more favorable conditions ("Resistant"). Single counts were of most value in showing the tuberculous condition only at the time of the count. Repeated counts were recommended to show the trend of the disease. Very few counts were "out of focus" with the actual condition of the patients. A deviation occasionally found was a slightly septic picture in a patient apparently handling his lesion well. Two patients had large lesions and only a hyperplastic blood-picture. Such cases were left in the balance for a later judgment.

Table 1 has been constructed, correlating the health status of the patients with their blood counts, in order to demonstrate the significant figures.

DEDUCTIONS

Those patients having Normal counts in 1929 are most often reported well now (88 per cent). Those with high lymphocyte counts (Resistant) add only slightly to this tendency (90 per cent).

The patients with Hyperplastic counts are less often well (82 per cent), and those with lymphocytosis in addition are somewhat better (89 per cent). A few more of those with Hyperplastic counts have had interval relapses than those with normal counts.

When the count was Septic, only 68 per cent are well, a progressive decrease from the percentage of the other types. This includes the benefactions of surgery. Those patients with Septic counts, without an increase in the monocytes (counts often only slightly abnormal), raised the average percentage of the Septic-count group which is well.

Those patients with a persistent, slightly Septic count (mentioned earlier) have a prognosis a bit better than those with a severely Septic count, a bit worse than those with a Hyperplastic count, and considerably worse than those with Normal counts. The two patients who had large lesions and Hyperplastic counts are now listed as "Well" (1).

The Chronic tuberculous class included a disproportionately large number of Septic counts (72 per cent); relatively few of the patients with Normal counts (7 per cent) and those with lymphocytosis (5 per cent) are listed as Chronic; and 27 per cent of all surgical cases are listed as chronically tuberculous.

Twenty-two patients are dead, twenty due to tuberculosis. The

ingly, the character of the primary tuberculous infection in the human lung. It was thus settled that the tubercle bacilli produce first a small focus in the pulmonary parenchyma usually in a subpleural position, and then secondarily, though rather immediately, infect the regional lymph nodes.

Examining a great number of cases of primary tuberculosis, Ghon and his co-workers studied in detail the histological picture of the primary *Affekt* and the methods of spread, not only in the lung, but also in cases in which the lung was not the first infected organ. They showed that the histological picture of the primary focus and the spread to the regional lymph nodes are entirely independent of the entrance of the initial infection. Regardless of whether the lung, intestine, skin, mouth, nose, and eye are first infected, the lymph nodes tributary to the respective organ are soon distinctly involved.

Ranke, in 1916, designated the term *Primary Complex*, to include the first focal lesion and the lesions in the regional lymph nodes.

In the United States, Opie examined radiographically as well as anatomically the primary focal lesion and confirmed the studies of Parrot, Küss and Ghon.

An analysis of the data amassed, until now, on the pathology of adult tuberculosis is neither an easy nor a fruitful task. Where the morphological findings of primary tuberculosis tend to be more or less clear and definite, the routes of spread and the anatomical manifestations of adult tuberculosis appear perplexingly multiform. Each case of adult tuberculosis, from the pathologist's point of view, is an involved and distinctive problem in itself. To give an exact answer in any instance concerning its relationship to primary infection is sometimes extremely difficult. To evaluate accurately in a given case the relative importance of endogenous metastasis or exogenous superinfection is often impossible; it is generally much easier to eliminate special routes of infection than to prove a definite method of spread.

Up to the present, a great deal of the explanation for the complex anatomical and reactive variations of adult pulmonary tuberculosis has been based on generalizations drawn from animal experiments, rather than on findings from systematic postmortem studies. For instance, the belief is popularly held that the varying course and structural expressions of adult tuberculosis are entirely determined by different stages of specific allergy which exist in the individual. In other words, the adult is said to respond like the animal whose type of reaction depends upon whether it has been previously infected. Further, experiments with superinfection have fostered and substantiated the idea that the postprimary tuberculous process of the adult is that of a localized parenchymal reaction in contradistinction to the first infection with its immediate spread through the lymphatic channels to the nodes.

Important as experiments are in explaining the immunological problems of animals, they are apt to be, I believe, less valuable, even sometimes mis-

leading, when applied to human tuberculosis. To date, it has proved impossible to produce in an animal a calcified complex. Yet, in considering adult human tuberculosis, such a complex appears to possess some importance as a lymphatic source for endogenous exacerbation. Further, as Schürmann and others have pointed out, in experimental work with animals, the individual constitutional factor of the human being (which is surely as important as exposure) can hardly be considered.

In an endeavor to solve problems of true reinfection and superinfection it would seem to me more promising to employ in a large number of cases the same anatomical method which enabled the French and Viennese Schools of Pathology to establish in so classical a manner our present knowledge of primary tuberculosis. Recently, Schürmann, studying anatomically one thousand cases of human tuberculosis, revealed illuminating data, and, at the same time, inferred how difficult, and even how dangerously fallacious can become the practice of explaining the findings of adult tuberculosis by experimental generalization.

In the German literature the Ranke theory, citing the dependence of different stages of tuberculosis on special allergic changes, retarded to a certain extent, for many years, progress in the objective investigation of the whole anatomical process of tuberculosis. Schürmann's study showed on a broad basis the impossibility of proving Ranke's idea that specific anatomical and histological forms of tuberculosis correspond always to different degrees of allergy.

From his anatomical findings Schürmann concluded that no inverse relationship exists between the intensity of the primary focal reaction and the degree of progressive lymph-node extension, and the subsequent occurrence or absence of phthisis. General miliary tuberculosis, however, is more often combined with a cheesy complex.

The belief is commonly held in this country that in an adult reinfection the tuberculous process in the lungs is strictly localized with no characteristic changes in the tributary lymph nodes. Schürmann stated that in a reinfection the tissue response, especially in the lymph nodes, is in principle usually not different from that in a primary infection. In his series of one thousand cases he pointed out that in the so-called postprimary lesion the regional lymph nodes are practically always involved. While diffuse cheesy changes occurred in only 14 per cent, isolated tubercles were noted in 42 per cent, and confluent tubercles in 37 per cent.

Opie has mentioned that acute miliary tuberculosis, when it occurs in adults, is not accompanied by calcified lesions in the lungs. In such a case the pulmonary disease possesses the characteristics of a first infection. General dissemination follows because the adult has not been made resistant by childhood infection. But Schürmann included 5 adults in the fifth, sixth

and seventh decades showing typical miliary tuberculosis and possessing still typical calcified primary complexes. In addition, he demonstrated that 25 per cent of all cases of progressive pulmonary tuberculosis, with bronchial and peribronchial spreads, illustrate distinct signs of generalized haematogenous dissemination. As a consequence of this anatomical evidence, it would seem necessary to modify the idea that haematogenous dissemination is always inhibited by a calcified complex.

The source of adult pulmonary tuberculosis has always been an open question. Much discussion has been concentrated lately, both here and in Europe, on the respective rôles of exogenous and endogenous reinfection, or, better, true reinfection, exogenous superinfection and endogenous exacerbation. Clinical experience points to the marked importance of exogenous superinfection. Leading authorities in the pathology of tuberculosis, such as Opie in United States and Aschoff in Europe, also stress that pulmonary tuberculosis in adults is acquired "from without." Simon felt, as to reinfection especially, that reinfection in the apical foci may be in a certain part haematogenous with a marked tendency to heal. Huebschmann found in miliary tuberculosis with meningitis isolated foci in the apices. Ghon pointed out that in so far as endogenous metastases are concerned the lymphogenous reinfection or exacerbation, especially in individuals above the fourth decade, is not uncommon. In Schürmann's series 45 cases showed lymphoglandular exacerbation. At this point I wish to make brief mention of a case published by Kudlich and Reimann which I saw personally in Ghon's Institute in Prague and which illustrates how difficult it often is to determine whether the reinfection has been endogenous or exogenous. A 19-year-old man showed acinous confluent tuberculosis in the middle and lower thirds of the right upper lobe. The apices were entirely free. The right bronchopulmonary lymph nodes regional to the right upper lobe showed cheesey tuberculous changes. The primary focus was about pinhead-sized and calcified, and located in the lower third of the left lower lobe. There were a few calcified "splits" in one left bronchopulmonary and one lower tracheobronchial lymph-node. These were found by radiographic examination. Shortly before the patient's death a tuberculoma was surgically extirpated from the postcentral gyrus of the frontal lobe.

The site of first superinfection has been generally placed in the so-called apex. Much confusion centres about the term "apex." As was recently pointed out by Anders, a pupil of Aschoff, it is not always made clear whether by this term the immediate summit of the lobe is meant or the upper third. Such a distinction ought to be made because a real difference exists in regard to superinfection. Superinfection (from without) occurs from 2 to 5 finger-breadths below the summit, while the small scars seen very often in both lungs do not occur more than one finger-breadth below. In Opie's experi-

ence latent apical lesions were found in 20 per cent of persons who died from causes other than tuberculosis. Schürmann reported a similar figure, 19 to 20 per cent. The age of these cases varied from 40 to 80 years. The apical lesion showed usually advanced healing. The beginning of the exogenous apical tuberculosis appears in some way dependent upon the bronchus involved. If the larger bronchi are involved, the foci are usually found infraclavicularly; if the smaller bronchi, third to fifth order, the foci are noted in the apex (summit).

The foregoing résumé of some recent pathologicoanatomical contributions to primary infection and adult tuberculosis emphasizes several points. It illustrates how far we still are from a clear understanding of the pathogenesis of human pulmonary tuberculosis, especially the adult type. The complex and varied character of adult tuberculosis is made obvious. That each case must be considered individually is stressed. The limitations of general principles drawn from animal experiments in explaining isolated cases of adult tuberculosis should be recognized. Similarily, the occasional interpretative difficulty which is present in the radiographic method of studying living lungs for statistics must not be overlooked. Though sincerely admitting that animal experimentations and roentgen-ray examinations of living patients can be useful in developing our knowledge of tuberculosis, I must still believe that systemic postmortem studies, linked with clinical data, can be of more value in offering us truths directly applicable to human tuberculosis For the anatomical method is based on the open study of actual tuberculous lesions in a human being.

A good international understanding of tuberculosis is also of importance in developing our knowledge of the disease. In the past, as Pinner mentioned, such an understanding has been somewhat hindered by the confusion which exists because the nomenclature differs so markedly in the American, French and German papers. It seems to be necessary that all the work done here and abroad should be known better on both continents. Views ought to be freely exchanged. Otherwise, as in the past, much time may be wasted and much good work may lose its scientific and practical usefulness. Witness the important contributions of Parrot on primary infection. Thirty to forty years elapsed before universal recognition and application were given to them simply because international coöperation was lacking.

In the second part of my paper I shall attempt to show the practical value of the anatomical method in the study of tuberculosis, as demon-

strated in postmortem work at the Buffalo General Hospital during the past two years. Even though the total number of cases has been admittedly small and the cases of progressive pulmonary tuberculosis have been few, careful routine anatomical observation and dissection have revealed several interesting features.

In the past, through the use of the scalpel and the roentgen film, few cases beyond early childhood have escaped in which no primary complex was demonstrated. To the universal anatomical incidence of primary infection medical teaching and general text-books still attest. With this fact in mind my figures of primary infection are of distinct interest.

Positive and negative findings of tuberculosis in p.m. examinations[3]

Primary infection

In limited age-periods:

	1 year	2	3-5	6-10	11-15	16-20	21-25
Negative	76	25	20	13	8	7	5
Positive	3	2	4	1	4	0	5

	26-30	31-40	41-50	51-60	61-90
Negative	6	7	7	2	3
Positive	6	17	26	32	53

In wider age-periods:

	3-20 years	21-30	31-40	41-50	51-90
Negative	48–84%	11–50%	7–30%	7–22%	5–6%
Positive	9–16%	11	17–70%	26–78%	85–94%

This group of figures is, of course, too small to permit any statistical conclusions. These findings, however, suggest several important and informative trends.

Anatomical studies in the past have given the impression that practically all individuals beyond early childhood show a primary tuberculous infection. In Philadelphia Opie found 90 per cent of his cases up to 18 years of age positive for primary tuberculosis; Pagel in Germany 58 per cent.

Numerous surveys carried out among school-children with the tuberculin test to show the incidence of primary tuberculosis have not confirmed the universal occurrence of infection as shown by the anatomical findings mentioned. Veeder and Johnston in St. Louis, using the

[3] Further systematic work since the acceptance of this paper for publication showed approximately similar figures for children and young adults. The number of positive findings at 25–50 years was, however, higher. These findings will be reported in the near future.

Pirquet test on 1,321 children, demonstrated 48 per cent positive at 13 years. Testing children in rural Minnesota, Slater found in two series of 1,654 and 1,000 children, 10 per cent and 13.3 per cent infected respectively. Korns showed 10.2 per cent infection among 1,103 healthy school children in Cattaraugus County, New York. Smith at Bellevue Hospital, New York City, obtained 1,286 positive tuberculin tests in 7,668 children tested. Chadwick and Zacks testing 100,000 and 42,000 school-children in Massachusetts procured 28 per cent and 20 per cent positive reactions.

My figures then verify from an anatomical basis those obtained by many observers with the tuberculin test. In Buffalo a tuberculin-test survey among school-children, age 6–18 years, showed about 17–18 per per cent with positive reactions. It must be mentioned that Opie and his workers found in 4,107 children 38 per cent positive tuberculin tests at 5 years of age, 71 per cent at 11 years, and 81 per cent at 15 years.

Further analysis of my figures shows an increasing number of primary foci after the age of 20 years. For example, at 30 years 50 per cent, at 50 years 65 per cent, from 51 to 90 years 90 to 94 per cent. (In reviewing my material 100 autopsies on adults were disregarded. In these, routine dissection did not reveal a focus or lymph-node change. No radiographic films were taken, however, in these cases, and in some the lungs were perhaps not so thoroughly examined for tuberculosis because of other marked pulmonary lesions, for example, carcinomatous metastases, pyaemic abscesses, infarcts, pneumonia and bronchial carcinoma.)

These figures concerning primary infection raise again several questions. How important are the geographical and social factors in the study of primary tuberculosis? May not the primary infection occur after the 20th or even the 30th year? Are we justified in entirely assuming that late primary infection must be of a severe character and rapidly progressive in course, resembling the tuberculosis of infancy and early childhood? It is usually impossible to determine in adult cases when the primary infection first took place, because in almost all cases the primary complex is calcified. The findings in two instances, however, seem to point definitely to a late primary infection. Two cases, one aged 65 years, the other 66 years, showed fibrous and fibrous cheesy tuberculous complexes. No calcification was noted. In one of these cases a few tubercles in the surrounding subpleural tissue were observed. I wish to mention also the incidental autopsy findings of a recent tuberculous infection in a girl 21 years of age who died from puerperal septicaemia.

In this case I

with a similar und a nut-sized fibrocaseous focus of nodular appearance

The frequen ion in one of the regional bronchial lymph nodes.

table: of the site of the primary complex is shown in this

	61 cases complete		
Left upper.....		Right upper.....	11
Left lower.....	20	Right middle.....	6
	17	Right lower.....	11
	Two foci		
Left upper.....		Right middle and upper.....	2
Left lower.....	3	Right and left upper.....	1
	2		
	Three foci		
Left upper and lower			
	1		
No foci in apices.			

My experience with .

necessarily small, becaus al cases of pulmonary tuberculosis has been to the Buffalo General l dvanced cases of tuberculosis are not admitted

In the present series spital.

tuberculosis, aged 29, 44 ree cases died from progressive pulmonary progressive acinous tuberc nd 45 years. In each, cheesy cavities and tubercles in liver, spleen osis were found. All showed haematogenous lymph nodes tributary to l kidneys, with tuberculous changes in the lymph-node changes were e respective organs. In one case calcified had taken place many yea ved. In other words, the first infection

Two cases showed incident reviously.

lymph-node tuberculosis. In y at autopsy severe calcified generalized a small tuberculous focus in ne of these, a colored male, 26 years old, adrenals were noted. e lung and marked tuberculosis of the

In regard to the source of

a few isolated examples. Two berculous reinfection my material offers superinfection or perhaps even es suggest strongly a distinct exogenous case, a white man, 48 years of a rue exogenous reinfection. In the first chus, calcified lymph nodes we who died from carcinoma of the bron- addition, a cherry sized fibroc found in the right upper lobe and, in lobe with fibrocaseous changes ous focus was noted in the left lower were free. The second case, a a regional lymph node. The apices coronary thrombosis, exhibited a man, 52 years of age, who died from ed calcified primary complex in the

left lower lobe. In the right lower lobe a fibrocaseous focus with beginning calcification was seen, with fibrocaseous changes in a regional lymph node. It is possible that these two cases represent a distinct reinfection, as anatomically the first infection appears healed. The reinfection takes on the structural character of a primary infection. Schürmann mentioned one case in which the secondary exogenous reinfection involving the intestinal tract produced the picture of a so-called primary complex.

As to the question of superinfection, there was observed a typical case of calcified complex in the right middle lobe along with recent tuberculous cavities in the subapical part of the left lung. The apex itself was not involved in the tuberculous process. The patient died with lobar pneumonia.

Another case raises the question whether the occurrence of a primary complex in every case of tuberculosis should be considered as a scientific dogma. In this case, a white female, 23 years of age, I found at autopsy an extensive cheesy pleuritis on the left side involving the diaphragm and mediastinal pleura. Generalized miliary tuberculosis was present. All the bronchopulmonary and tracheobronchial nodes were examined and found to be not involved grossly. Only in a few of these nodes were microscopic tuberculous lesions seen, apparently in connection with the miliary tuberculosis or pleuritis. With the exception of one large pea-sized cheesy somewhat fibrous focus situated immediately subpleural to the mediastinal surface of the left lower lobe, no other focus was discovered which possessed the characteristics of a primary focus. Radiographic examination of the lungs postmortem was negative. Calcified lesions in the lymph nodes were seen nowhere in the body. In this case we have to discuss the probability that an overwhelming first infection may infect the pleural cavity at once. For careful dissection of all organs, especially all lymph nodes, revealed negative findings in the direction of a primary extrapulmonary infection.

One case in my material is significant in illustrating the difficulty of determining the site of primary infection. Here in a 36-year-old white male I found marked cheesy tuberculosis of the upper mesenteric lymph nodes adjacent to the duodenum and inferior to the head of the pancreas, with extensive tuberculosis of the periaortic lymph nodes and posterior mediastinal lymph nodes, with involvement of the thoracic duct. Diffuse miliary tuberculosis was present. No primary complex is found in the lungs; the left bronchopulmonary and upper tracheobronchial lymph nodes, however, showed cheesy changes. These changes, though, were

slight in comparison to those in the abdominal
The apices of the lungs showed large nodules neriaortic lymph nodes.
small cavities. ginning formation of

In respect to postprimary changes, such as s
lous lesions, in the lungs my material presents t and healed tubercu-
llowing figures:

61 cases with typical comple:

41—no other tuberculous changes.
20—15 scars or fibrous cheesy lesions, in the upper
5 haematogenous tubercles in liver, spleen and of upper lobe.
uls.

11 cases with old primary foci but without mentio

9—no other tuberculous lesions. *ph-node changes*
2—scars in apices.

28 cases with old, mostly calcified changes in bronchop
bronchial lymph nodes; site of primary focus n ry or tracheo-
ioned

18—no other lesions.
7—scars or fibrous tuberculosis in the apices.
2—calcified or cheesy lymph nodes in the mediastinal a
1—apparent exogenous superinfection. creatic chains.

Summary: 100 cases.
68 showed primary infection restricte
primary complex and no other les e so-called
24 showed localized tuberculosis or fib
apices. s in the

In regard to intestinal tuberculous infection, 4 cases
years) showed fibrocaseous or calcified changes in the lo 31, 40
lymph nodes. In one case calcified nodules were also found i enteric
bronchial lymph nodes, and in another case one small c acheo-
was found in a subpleural position in the lung without node
changes. -node

SUMMARY

The importance of careful systematic postmortem exan
human tuberculosis is stressed. The changing views in the n in
literature of post primary tuberculosis are pointed out. The ent
of tuberculous foci in children and young adults in the reporte age
has been found to be comparatively small. A few isolate rial
of

apparently exogenous reinfection and a few very unusual cases of fatal primary tuberculosis in young adults are recorded.

Note: I wish to thank my assistant, Dr. S. Sanes, for his help in reviewing the postmortem protocols in this study.

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PRIMARY TUBERCULOSIS AMONG NURSES[1,2]

EVERETT K. GEER

Nearly two years ago, before the Mississippi Valley Sanatorium Association, I presented the results and conclusions drawn from an investigation concerning the incidence of tuberculosis among student nurses at Ancker Hospital in St. Paul. Although that paper has been published in full (1), I shall here present the salient points as a background for the present discussion.

From 1920 to 1928 the records of the Nurses Training School at Ancker Hospital showed an incidence of 4.5 per cent of tuberculous disease among its nurses. This was three times the normal expected incidence among young women of the same age-group.

In September, 1928, routine intracutaneous testing was done on all incoming nurses, using 0.1 mgm. O. T. as the initial dose and repeating in 48 hours with 1 mgm. if no reaction occurred. Those nurses found negative to 1 mgm. have been retested every six months until they have become positive. X-ray films of the chest have been made routinely on entering training and again after the nonreactors became reactors.

It was found that, on the average, 30 per cent of the nurses were reactors on entering training and close to 100 per cent reacted before their training was completed.

Of the 112 new young women entering training from September, 1928, to September, 1930, 6, or 5.5 per cent, developed tuberculous disease. Three of these had pleural effusions, two parenchymatous lesions of the adult type and one a parenchymatous lesion of the childhood type. Five had no reaction to 1 mgm. O. T. given intracutaneously when they entered training.

A comparative study of the nurses in 5 other St. Paul hospitals showed an average incidence of tuberculous infection of 42 per cent in the third year of training and no cases of tuberculous disease in the two-year period which was under consideration.

[1] Read at the twenty-eighth annual meeting of the National Tuberculosis Association, Colorado Springs, Colorado, June 9, 1932.

[2] Aided in part by a grant from the Ramsey County Public Health Association.

These facts seemed to warrant unusual suggestions to the Ancker Hospital authorities. It was recommended (1) that a strict medical aseptic technique be instituted in the tuberculosis department; (2) that single chest roentgenograms be made of all patients entering the hospital; and (3) that sputum from any and all patients be sent to the laboratory routinely by nurses.

The establishing of an adequate aseptic technique required time and money and was finally in full effect, from the standpoint of protection to the staff, nurses and employees, early in the spring of 1931. During the several months of preparation more stress than ever was placed on observing the precautions that had been used for many years. The second and hird suggestions have not been carried out as yet for various reasons, hich now appears to have been for the best as the value of an aseptic chnique stands out more clearly.

Miss Birgit Tofte, R.N., supervisor of the contagious department at cker Hospital, developed the technique now used in the tuberculosis artment. She describes the changes made and the technique as ows:

> technique which is now being carried out at the Ancker Hospital tuber- sis department is not that of segregation of individuals or groups of pa- s such as is used when we deal with many types of infections; for example, ommunicable disease hospital or department where each disease is cared separate units. Since we are dealing with tuberculosis only, the small- hnique is unnecessary. However, an equally rigid technique is other- blished.
>
> ovations that were made were many:
>
> 1: [illegible] at the department the kitchens were given a thorough house-cleaning and there- [illegible] as clean uncontaminated areas.
>
> [illegible] of food having been in contact with the patient are permitted in the kitchens or
>
> 3: [illegible]. All patients are absolutely prohibited from entering the kitchens. Food a[illegible] patient from the outside must be consumed at once.
>
> bo[illegible] cabinets were given a thorough cleaning and made clean uncontaminated
>
> 4: [illegible] bottles were thoroughly cleaned and supplied with new corks. All paper
>
> 5: [illegible]ced with new ones.
>
> are [illegible] were cleaned out and supplied with fresh uncontaminated linen.
>
> 6: [illegible]-washing plant was established on the basement floor. Contaminated dishes trol[illegible] on dish-carts and taken direct from the patients' rooms to the dishwasher.
>
> 7: [illegible]ds throughout the department were revamped by installing foot-pedal con- tient[illegible] found to be quite efficient for isolation-technique use.
>
> [illegible]ons were thoroughly cleaned and aired. All stationery, records, and pa- [illegible]erilized by steam, and thereafter treated as clean uncontaminated articles.

8: Signs were placed about as reminders, instructing all those concerned, the patients, visitors, maids, orderlies, and medical and nursing staff as to these clean areas.
9: Supervision was reinforced at this time in order to teach everybody concerned what to do.
10: All floors throughout the building were considered contaminated.

The technique now used is as follows:

The Nurses: Upon going on duty in the tuberculosis department, the nurses go directly to their dressing-rooms, where they remove the school uniform and cap, and put on a skull-cap completely covering the hair, and a short-sleeved cover-all white dress.

The wrist-watch is fastened above the elbow. Then, when working with the patients at the bedside or in dressing-, utility- or dining-room, the nurses wear a mask, covering mouth and nose. The mask is made of several layers of fine-mesh gauze, which has been tested and found sufficiently fine to prevent the filtering through of secretion from direct spray of the patient.

A short-sleeved surgical gown is used at all times while working in the contaminated area at the bedside, in utility-, treatment- and patients' dining-room. Upon leaving a contaminated area, the nurses scrub hands and arms thoroughly, and then remove gowns in such a manner as to prevent recontamination of hands and arms. The gown is then folded, clean side out, and hung in a clean area set aside for that purpose. Then a second scrubbing of hands and arms is done, washing from above the elbows downward.

The nurse in charge of medicines prepares the medicine tray; then she puts on a gown and serves the medicine to the patients. Glasses and tray are washed and boiled before they are put back in the medicine cabinet. The procedure of scrubbing and gowning is carried out always.

Whenever a nurse leaves the department, she goes to the dressing rooms where she removes skull-cap and short-sleeved white dress, and dons her school uniform, after having washed face, arms and hands well.

Serving of Food: Nurses serve all meals to the patients. The food is brought to floors in electrically heated carts. Nurses, properly gowned and masked, carry the trays to the patients, both in the wards and to the up-patients in dining-rooms.

The Medical Staff and Internes: Doctors and internes remove coat, roll up sleeves and put on skull-cap, mask and surgical gown, which are used while making rounds. Previous to starting rounds the physician receives reports of patients' condition, etc., and checks the charts. Charts are not brought to the bedside. The supervisor, who remains clean and uncontaminated, takes notes dictated by the physician. The physician, upon completing rounds, removes cap, mask and gown and scrubs thoroughly. Then notes are transcribed to charts at the desk.

X-ray Depar
department
The X-ray p
adjusts the p
the bedside u
he goes into
clean pillow-
the machine
ing the plate
the clean plat
and arms are

chnique: The patients who are taken to the X-ray
oved from the cart if they are ambulatory cases.
ed into a clean pillow-slip and the nurse in charge
ray technician need not handle the patient. Where
X-ray technician wears a cap, mask and gown, as
ne nurse adjusts the plate which is covered with a
of the bed is draped with a clean sheet, so that
in contact with the bed-clothing. Upon remov-
ns up the pillow-slip and the technician removes
ing, cap, mask and gown are discarded and hands

Laboratory T
gown, and ca
after use. Pi

oratory technicians also wear mask, cap and
me technique. Syringes and needles are boiled
oughly cleansed and put in 70 per cent alcohol.

Maids and Or
hands, arms a
plained to the
spend a great
and gowns whil
and wash thor

nd orderlies are taught how to gown and scrub
ghly. Modes of disease dissemination are ex-
isors, who have complete charge of these people,
aching them. Orderlies and maids wear caps
on going off duty, they remove caps and gowns

Soiled Linen: T
of the equipmer
put directly int
large truck and
the linen is sorte
it is emptied dire
uses cap, mask, go

collected in canvas hampers, which are a part
doing the bedside work. The soiled linen is
These are then collected by an orderly on a
erculosis-department sorting room. Here
s and then brought to the laundry where
her. The orderly who handles the linen
loves.

Dishwashing: The s
dish carts, which ar
dishes are stacked a
orderly runs the dish
back to the diet kit
wear gowns. They
vention of recontam

trays are collected from the wards on to
dishwashing room by an orderly. The
e washer by one orderly, and another
oves the sterilized dishes, which are sent
or. The orderlies who wash dishes also
ted in the importance of technique, pre-
, etc.

Elevators: The eleva
ator wears a gown w
bing hands, etc., up

ment is used by everybody. The oper-
is also taught the importance of scrub-

Articles Made by Patients: Articles made by the patients are washed, sunned or sterilized before they are removed from the department.

Personal Laundry: Personal laundry, which is sent home for washing or sent out to public laundries, is placed in clean paper bags. Those who call for laundry are instructed to empty contents of the bag directly into a boiler with cold water, and then boil for twenty minutes.

Garbage: The garbage is burned after each meal.

What I hoped for from an effective technique was a reduction in the incidence of tuberculous disease. So far this reduction has been satisfactory, for only three (all nonreactors as new students) out of 181 nurses entering training since September, 1930, have developed clinical tuberculosis, a percentage incidence of 1.6. Their history abstracts are as follows:

Case 1: Miss B. M. S., age 22. *F. H.:* Unimportant. No known contact before training. *P. H.:* Diphtheria, October, 1931. Entered training in September, 1930. No reaction to 1 mgm. O. T. In March, 1931, had 4-plus reaction to 0.01 mgm. O. T. Physical examination and X-ray film of chest negative. *P. I.:* About February 1, 1932, began to tire easily and cough a little. Her weight began to fall. On March 6, X-ray films of chest showed definite parenchymatous lesion in left upper lobe. No abnormal physical signs. No sputum.

Case 2: Miss D. P., age 20. *F. H.:* Unimportant. *P. H.:* Unimportant. No known contact before training. Entered training in June, 1931. No reaction to 1 mgm. O. T. Physical examination and X-ray film of chest negative. In December, 1931, had 2-plus reaction to 0.01 mgm. *P. I.:* On April 1, 1932, developed an acute tonsillitis from which she recovered quickly. On April 23 had an apparent upper respiratory infection with sharp pain in left upper chest. On April 29 X-ray film of chest was clear. On May 2 there were physical signs of fluid with confirming X-ray findings. She had no fever from April 23 to April 29, after which she began having fever ranging from 100° to 102°. Aspiration was delayed to May 17 at which time no fluid could be found. X-ray film of chest showed it practically gone.

Case 3: Miss H. G., age 19. *F. H.:* Unimportant. No known exposure before training. *P. H.:* No serious illnesses. Entered training January 4, 1932. No reaction to 1 mgm. O. T. Physical examination and X-ray film of chest negative. *P. I.:* On February 15, 1932, became ill with erythema

nodosum and was sick in the h... April 20 and did not feel well... running fever of 99.4° to 100.4°, ... Returned to training on ness. Physical examination wa... readmitted as a patient, definite adenopathy at right root... malaise and feverish- 3-plus. On May 17 she had signs... film of chest showed chest confirmed this. Aspiration r... 0.01 mgm. O. T. was No guinea pig report to date. Is sti... chest. X-ray film of ...egative to culture.

The results so far should not pr... ...tely ill. the variations observed by Shipma... ...lasm because of dence of tuberculosis among nurses ... the annual inci- However, the hope I expressed two y... ... of California. into a conviction, and that hope was ... ...lly crystallizing ... he communica-

TABLE ...

Showing a combined tabulation of tests of student n... St. John's, St. Joseph's and St. Luke's... April and May, ... , Mounds Park, ...in

YEAR IN TRAINING	NUMBER TESTED	...ER AND PER VEGATIVE
		per cent
First	119	69.3
Second	136	59.6
Third	141	71.0
	396	

bility of tuberculosis to nurses and setting up an ... in the form of a rigid technique, the incidence ... could be reduced at least to the expected percentage ... possibly lower. As yet, I do not feel anything has ... than two years is necessary to prove anything having ... common denominator. But the trend appears signific...

As I intimated in my first paper, I have been X-r... routinely as their skin reactions have become positive. ... produced nothing. Now I am X-raying all nurses as the ... ing. The results of this study will be published in due tim...

It was thought advisable to retest the other training sc... Paul, to see if any marked change had occurred from the findi... The results of this testing, as shown in table 1, show no vari... those of two years ago. During this last two-year period 4 nu...

these other training schools in St. Paul have developed tuberculous disease, a percentage incidence of 1.01.

The accompanying chart shows the results of the periodic testing done on the nonreactors for the past four years. It is interesting to note that after September, 1930, the upward curve, so striking in the two preceding years, is beginning to be less abrupt, although it appears that even with an aseptic technique nearly all of our nurses will leave training at the end of three years as reactors. To me this is not at all alarming, as no intelligent nurse or physician either can hope to pursue her or his profession without eventually coming into contact with tuberculosis. And I am still old-fashioned enough to believe that most available evidence points strongly to the contention that primary tuberculous infection, if not massive or frequently repeated, in the vast majority of individuals leaves behind it the benign influences of immunity rather than the malignant aspects of allergy.

The thought of establishing a strict medical aseptic technique in tuberculosis sanatoria and tuberculosis departments of general hospitals found disfavor and frank opposition in the minds of many when I suggested it in 1930. The objections were, first, that it was unnecessary, the contention being that precautions used in the average tuberculosis institution were adequate and that tuberculous infection anyway was not dangerous *per se*, as it required infection *plus* to produce disease. The obvious answer to this objection is that, at Ancker Hospital prior to September, 1930, the preventive measures employed by nurses were distinctly above the average, but this was not enough in view of the material, virgin to tubercle as it was, with which we were dealing. Apparently disregarded was the fact that heavy infection with tubercle bacilli frequently repeated needs no *plus* to produce disease.

Another objection was that it would upset patients and make them feel that they were being cut off from the world "almost like lepers." Experience has shown this fear quite without foundation. Actually the big majority of patients have been most coöperative and interested. They and their families and friends are being reminded repeatedly that tuberculosis causes tuberculosis, that prevention is possible, and that eternal vigilance is the price of safety.

Another idea entertained by some was that nurses would be unfavorably impressed and even frightened, and that the Ancker training school would have difficulty in filling its quota year by year. Here again we have noted just the opposite. The nurses have responded beyond ex-

pectation; as a group they appreciate the precautions set up for their benefit. Some of the negative reactors are even vying with each other in observing the technique meticulously, to see if they cannot go through

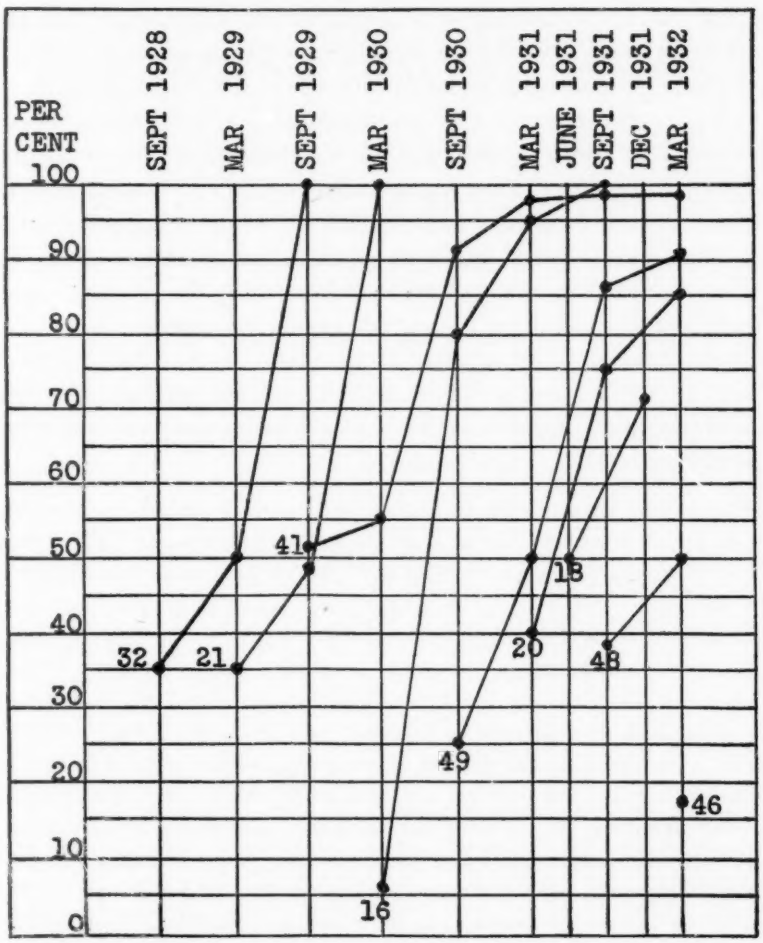

CHART 1

training and remain negative. This is indeed a strange exhibition of the fear and hysteria which some predicted we would create and encourage.

This work, now extending over a four-year period, is apparently not going to be alone in pointing out the necessity for more adequately protecting young adults coming into intimate contact with open tuberculosis.

The work of Hetherington (3) and his associates, dealing with tuberculosis among medical students and showing the marked increase of apical lesions as the students progressed in their medical course, is most significant. What other explanation could there possibly be for their being "peculiarly subject to advanced tuberculous infection" than that their work offered the opportunity for coming into intimate contact with the tubercle bacillus without adequate protection being afforded them.

Does it not seem strange in a year when our slogan is *Tuberculosis causes Tuberculosis* that there should even be one dissenting voice toward an appeal, supported by an increasing volume of evidence, for more adequate protection against frequent and massive infection with the tubercle bacillus among our medical students, internes, nurses and other hospital employees? And does this not seem more strange in the light of our present knowledge which teaches us that the only proved factor, without which one cannot develop tuberculous disease, is tuberculous infection?

Stewart (4) has come to a full appreciation of the problem as it applies to general hospitals, judging from his remarks before the American Hospital Association in 1931, when he stated,

> I have suggested that hidden infections in general hospitals is a growing danger to young members of the staff, especially pupil nurses. The reason is that these young people are not as well prepared to meet these infections as they used to be. Twenty or more years ago tuberculosis was common in all communities, so that young people could not grow up to adult life without encountering it, and having a chance to build up some resistance against it.
>
> But now conditions are different. Known spreaders of infection are largely segregated in sanatoria or hospitals or are taught to be safe or at least safer at home. At the present time young people in good homes and in careful communities can grow up with scarcely enough acquaintance with tuberculosis infection to build up any defence against it. In a gathering place of tagged and untagged infections, such as a general hospital, such unprotected young people are as sheep among wolves. The danger of these more carefully brought up young people in the more carefully managed hospitals today may be greater than the danger of their less carefully brought up predecessors of twenty years ago in the less carefully managed hospitals of that day. Times and conditions have changed and we must change with them.

But why not apply this to sanatoria as well? Is the tubercle bacillus in a sanatorium any different from that in a general hospital? Does the name "Sanatorium" have any peculiarly inherent protective virtue? Does the relatively care-free, careless, young adult suddenly acquire

habits otherwise foreign to his nature just because he is working in a sanatorium?

It unquestionably is true, as Baldwin (5) believes, that this particular problem varies in different communities and in different institutions. Many elements enter into this variance. The age of the individual nurse will be an important factor and the element of previous nursing experience must also play a part. In institutions such as Trudeau, White Haven, Pokegama and others which have nurses training-schools consisting chiefly of ex-patients, one will find quite a different phase of tuberculosis than that encountered in a school such as at Ancker Hospital where over two-thirds of the students on entering training are still children as far as contact with the tubercle bacillus is concerned. The first type obviously requires thought directed toward relief of physical strain or anything else which might induce prolonged fatigue. The second type just as obviously demands strict measures directed toward preventing massive infection, and these measures must be far superior to those one finds in the average sanatorium or general hospital to-day.

CONCLUSIONS

1. Of 181 nurses entering training at Ancker Hospital, Saint Paul, Minnesota, from September, 1930, to the present time, three have developed tuberculous disease, a percentage incidence of 1.6, two having pleurisy with effusion, and one a parenchymatous lesion of the adult type.

2. The 3 nurses who became ill did not react to 1 mgm. O. T. given intracutaneously on entering training.

3. A medical aseptic technique described in detail has been in force since early in 1931.

I am indebted to Drs. C. H. Matson, Gordon E. Strate and J. Allen Wilson of St. Paul who assisted me with some of the testing.

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OBSERVATIONS ON PULMONARY TUBERCULOSIS AMONG MEMBERS OF THE SAME FAMILIES

PAUL DUFAULT[1] AND DANIEL ROBINSON[1]

Those engaged in the field of tuberculosis are often struck by the pathological similitude found clinically and roentgenologically in members of the same family. In 1902 Baldwin reported the experiments of Turban, who remarked that, in 55 families, 80 per cent of the individual members showed evidence that the disease had originated in the corresponding lung. After a survey of his own, conducted on 65 families totaling 166 individuals, Baldwin found that 70 per cent had developed pulmonary tuberculosis in the corresponding side. In 28 families where there was parental tuberculosis 78 per cent had children with homolateral disease. In one family the father and four children had the same lung affected first. In 35 families with one or more tuberculous brothers (parents not affected) 63 per cent had the disease homolaterally.

Fishberg has observed that "in about two-thirds of the cases, the side affected is the same in the several affected members of the family," and in explanation uses the theory of *locus minoris resistentiae.*

Lately, Gardis and Joannette cited a few striking cases in the *Journal Médical de Leysin.*

No place is better suited for a study of this kind than a State Sanatorium, where whole families come for treatment or examination. Accordingly, the records of 26 family-groups were exhumed from our clinical and X-ray files. The histories were studied from the following viewpoints: Age of onset, date of first symptom and its nature, and course of the disease in regard to haemoptysis, fever and outcome. We then turned to the films and considered the side of the lesion, its location and character, and the presence or absence of calcification and cavitation.

Age: The age given is that of the patient at the time his symptoms appeared, and is calculated from the history given. For instance, a 30-year-old patient may have had symptoms of tuberculosis for five years without knowing that he had the disease. This would make the age of onset 25. There is here, naturally, a margin of error varying with the

[1]Rutland State Sanatorium, Rutland, Massachusetts.

accuracy, the memory and the reliability of the patient and with the nature of the symptoms revealed. It is easier to remember the precise date of an haemoptysis than the beginning of an insidious and slow-growing sense of fatigue.

In most instances the ages vary between 14 and 30. Nothing outstanding appears at first sight, as the incidence of onset is usually most marked at that very period of life. In some families all the members showed signs of illness before 20, or after 20, and even after 30.

Is this an indication of virulence or attenuation of germ, or of resistant or virgin soil?

When one of the parents is included in the group, there is naturally a marked difference in the ages.

First symptom: In only 9 families were the first symptoms similar; and seven of these reported colds or coughs. Fatigue was reported by one family and haemoptysis by another.

In general, the greatest variety and dissimilitude possible were shown. In 2 families, each having 5 members, no two members had the same initial symptom.

Haemoptysis: In 11 groups haemoptyses were either present or absent in every case; in the remaining 15 families, some members had haemoptyses and others not. Of the 60 individuals 28 had haemoptyses.

Date of onset: In only one group was the date of onset found to be in January and May of the same year. In one family, one child showed symptoms in January, 1929, and three others in March, 1930. The mother had already been ill since 1923, and the father had died of tuberculosis in 1929.

In the majority of the other groups a period of one to five years elapsed between the onset of illnesses.

Fever: Eleven groups are febrile and seven afebrile; that is, every member composing the group had or did not have fever at some time or other during the disease. Thirty-two of the 60 individuals had fever.

Outcome: Of the 26 families, 11 became quiescent, 1 improved, 1 died and 13 differed. Of the 60 individuals, 42 (70 per cent) became quiescent, 4 (6.6 per cent) were improved, 1 (1.6 per cent) remained active, and 13 (21.6 per cent) died.

Of the families in which the right lung was first affected, 5 became quiescent, 1 improved and 4 differed. Of the 23 individuals in these families, 16 (69.5 per cent) became quiescent, 4 (17.4 per cent) improved, and 3 (13 per cent) died.

Of the families in which the left lung was first affected, 2 became quiescent, 1 died, and 6 differed. Of the 19 individuals in these families, 11 (57.9 per cent) became quiescent, 1 (5.3 per cent) remained active, and 7 (36.8 per cent) died.

Of the families in which the initial lesions differed, 4 became quiesent and 3 differed. Of the 18 individuals in these families 15 (83.3 per cent) became quiescent, and 3 (16.7 per cent) died.

It will be noted that there is a difference in the outcome of the various cases, apparently depending upon the side first affected.

X-ray films: A study of the films is much more accurate, and consequently of considerably greater interest and value.

We examined carefully the first films taken on each individual in order to have as good a point of comparison as obtainable, and also in an attempt to observe the lesions from their very beginning. Unfortunately most of the cases were already in the second stage (National Tuberculosis Association Classification), and some had even reached the third stage; so that the initial lesion was overshadowed by secondary phenomena such as fibrosis and cavitation. In practically all instances the infection had also spread to the other side with its accompanying pathological effects, sometimes making problematical the determination of its point of origin. It is usually taken for granted that the side showing the larger amount of fibrosis and pulling is in most instances the first involved, and this principle was followed.

The oldest lesion is not necessarily the largest; neither may it be the most important at the time of admission. This point is illustrated in one of our series of films.

Side: The initial lesion was found, by X-ray, on the left in 9 families and on the right in ten. In the individuals of the remaining 7 groups, the lesions were located either on the left or on the right.

There is here a striking similitude. The fact that in 9 of these groups the lesions are located on the left side seems significant, inasmuch as, in the majority of cases at large, the first side affected is the right. The X-ray films show bilateral lesions at present, but it is usually easy to determine the side primarily involved by the amount of fibrosis and the changes it has brought about.

The lobes involved and the type of the lesions,—caseous, fibrocaseous, etc.,—offer no particularities.

Calcification: Calcifications are seldom seen (5 in all) and never in two members of the same family.

Cavities: Cavities appear in most of the films.

SUMMARY

From the family histories we learn that the age of clinical onset in many families is approximately the same; that in 13 families the dates are two years or less apart, and within five years of one another in 21 of the 26 families. The first symptoms, and the recorded haemoptyses and fever as well, seem to have no particular significance. We also find that 11 of the families became quiescent, 1 improved, 1 died, and 13 differed.

We obtain from the films a more accurate picture. The left side is first affected in 9 groups, the right in 10, and either the left or the right in the remaining 7 groups. Seventy per cent of the 60 individuals show homolateral disease.

It is not until we combine the family histories with the interpretation of the films that we obtain striking differences. In the families in which the left lung was first affected, we find that 36.8 per cent of the individuals died, while, when the right lung or either lung was first attacked, the death-rate was only 13 or 16.7 per cent, respectively. We also find that, when the initial lesions differ, the average time between the first breakdown in the family and subsequent breakdowns is 8.8 years, while, in the families whose right or left lung is first attacked, the average time is 3.8 and 3.5 years, respectively. In addition to the apparent superior resistance to infection possessed by the former group, it also has the largest percentage of quiescent cases,—83.3 as compared with the average of 70 per cent.

Were these findings constant for larger groups, it is evident that useful deductions could be made in regard to the prognosis and the treatment of the disease.

BOOKS[1]

H. MORRISTON DAVIES: *Pulmonary tuberculosis: medical and surgical treatment. Demy 800, pp. 464, with 69 text figures and 77 radiographic plates. Cassell & Co., Ltd., London. Price 27 s., 6 d., net.*

By CHARLES W. MILLS

The title and subtitle of this book describe its purpose aptly. It is a general text-book on pulmonary tuberculosis with especial attention to treatment. Of its 348 pages, the first 88 briefly but clearly touch the high spots of pathogenesis, symptomatology and diagnosis, leaving 260 to be devoted to treatment. The shifting emphasis during recent years in the field of treatment is illustrated by the fact that in the sections on this part of the subject 120 pages are given to sanatorium, symptomatic, and so-called specific treatment, and to the treatment of complications, and 140 pages, over half, to surgical treatment. This might suggest a lack of balance in the book, but it is undoubtedly the author's purpose as indicated by his title. It is a general, rather condensed, book on pulmonary tuberculosis with especial devotion to surgical treatment,—although the author makes it clear that he does not push surgery when non-surgical methods will suffice,—and such being its scope and purpose the work is exceptionally well done. In fact it seems to the reviewer that from this

[1] THE REVIEW plans to carry a section devoted to *Book Reviews* from time to time. It accordingly invites contributions of this nature from any authors who may see fit to submit manuscripts and will be glad to accept those reviews that measure up to standards that would comprehend such features as thorough familiarity with the text of the work under review, as well as knowledge of the subject and field covered by the book; apposite comparisons with related texts; critical ability and treatment; good literary form; and helpful description of contents. Uncritical praise and repetition of publisher's "blurbs" will be as undesirable as savage or personal attacks; neither will be tolerated. The main—almost the sole—purpose of an acceptable review should be to inform and to entertain. No limits or restrictions will be set on length of manuscript or manner of treatment provided the above-mentioned general considerations are adhered to. All reviews must be submitted gratuitously and those accepted will be published without compensation. Manuscript should be prepared in standard form (typewritten, one side of sheet only, double-spaced, etc.), and according to the style set in the reviews printed above.

Any opinions expressed are to be considered as those of the reviewer alone, and the widest latitude consistent with probity, ordinary courtesy and fairness will be allowed in this respect. In no way are they to be regarded as representing opinions of the publisher or editors.

In general, reviews will appear under the reviewer's name, initials or pseudonym. If, however, good and sufficient reasons can be adduced, worthy anonymous or unsigned reviews may be published, provided the author's name is known to the editor.—*Editor.*

viewpoint it is the best one-volume text-book on the subject so far published, and that it fills a real need. It gives a clear, accurate, and very readable up-to-the-minute presentation of present knowledge on the subject.

In most of the present controversial questions in tuberculosis the author very fairly presents both sides, usually quoting authorities and perhaps stating his own preference. Of such may be mentioned his brief discussion of the rôle of allergy, the selection of a proper anaesthetic in thoracoplasty, and the one- or several-stage operation in thoracoplasty. His own stated preference for the one-stage operation is at variance with the views of most thoracic surgeons and may well be criticized. One omission also may be mentioned, which is that he does not discuss the present controversial question as to the relative importance of exogenous and endogenous reinfection and its bearing on prophylaxis.

The general sanity of his outlook may be illustrated by a few quotations. For instance: "Every patient shows his own particular variation and combination of immunity and allergy, of control and failure, or slow response or rapid loss of resistance, of slight or intense fibrosis and consequent mechanical change, or of mild or intensely acute reinfection. Every patient therefore has his own individual characteristics and no group classification will define him. It is this that must be borne in mind throughout when considering clinical manifestations and the treatment of any case of pulmonary tuberculosis."

And again in the chapter on artificial pneumothorax: "Sanatorium treatment must be regarded as the invariable line of treatment, and in most cases the first and only line to be adopted until the course of the disease and its response to treatment have been studied. Artificial pneumothorax is brought into use to supplement sanatorium treatment when it is felt that that alone is insufficient to arrest the disease."

Subtilely ironical surely is this statement regarding the much-abused calcium therapy: "Calcium is quite free from danger .... and can be given without fear of making matters worse. It is therefore of value for its psychological effect on the type of patient who requires no treatment other than complete rest, but who becomes unsettled and apprehensive because nothing which he considers definite is being done for him."

Such fetiches from the past, once accepted treatment and still lingering, especially with the general practitioner, as the insistence on fresh air to the point of exposure to extremes of cold and inclement weather, the abuse of forced feeding with its result either of excessive overweight or of digestive upset, and the use of direct heliotherapy in active cases, are properly condemned.

Special chapters by other authors on childhood tuberculosis and on specific therapy (including such things as tuberculin in its various forms, sanocrysin,

secondary vaccines, etc.) are well done. The discussion of the present status of tuberculin therapy is especially good. The generally negative results are emphasized. On the other hand the reviewer's feeling is that the author shows too much favor to sanocrysin, which will probably before long go to the graveyard with most of its brothers of the past. As the author himself suggests, it is probably only another form of shock therapy which he himself in general condemns.

In regard to the nonsurgical section of the book a few other minor criticisms might be offered, such as the frequent reference to the importance of secondary infection of tuberculous pulmonary lesions, especially cavities. The bulk of pathological evidence would seem to show that this is probably of rare occurrence. The continued use of the word *myocarditis* to mean apparently a weak or atonic heart muscle is also open to objection.

The cream of the book is in the surgical sections. The comprehensive and up-to-date discussion of the various surgical methods, even including such rarely necessary or applicable procedures as intercostal neurectomies, extrapleural pneumolyses, and scalenectomies, leaves little to be desired from the point either of first-hand knowledge of the subject or of clearness of presentation. The differential indications for the various collapse measures, used either individually or in combination, are well presented. The chapters on artificial pneumothorax are admirable. Phrenic paralysis, a method of great value in selected cases, but which has by indiscriminate and careless use undoubtedly been greatly abused of late in some quarters, is sensibly dealt with. Its routine use in connection with artificial pneumothorax and even with thoracoplasty is rightly condemned. The author apparently likes to use it as an end-treatment in terminating artificial pneumothorax. This may be good treatment, but Packard, in his recent excellent review of the subject and report of over 100 successfully terminated artificial pneumothoraces, states that he has very seldom found end-treatment by this method necessary. In the chapter on phrenic paralysis only a very small paragraph is given to the method of temporary paralysis. Surgeons are perfecting methods for easily recovering the nerve at subsequent operations and it is probable that this procedure will in the future be more frequently used in doubtful cases.

Thoracoplasty in its various forms is adequately covered. Criticism has already been made of the author's apparent penchant for the extensive one-stage operation,—certainly a dangerous procedure as past experience has proved.

In reading the chapters on intrapleural pneumolysis and oleothorax the reviewer gets the impression that the risk of these operations is rather lightly treated. The former is certainly dangerous except in the hands of a surgeon thoroughly skilled in its use. Its field of application is limited, but in selected cases it is unquestionably very efficacious and, as the technique is further per-

fected, its use will probably increase. A review of the literature on oleothorax would indicate that it may in the balance cause more trouble than it relieves, that simpler measures will usually serve as well, and that its use in the future will be less rather than more.

In a very good concluding chapter on the sanatorium of the future the author stresses the importance of measures to secure the necessary coöperation of medical, surgical, and hospital staffs,—a very live subject.

The book is very well made from a technical standpoint. There are numerous illustrations and many X-ray reproductions which are exceptionally clear. There is a good index and a sufficiently full bibliography at the end of each chapter.

To sum up, this would seem to be a most timely book, and one which can be recommended heartily to any interested in the subject. Surgical treatment, meaning all forms of collapse therapy, has been by all odds the greatest development in phthisiotherapy in the past twenty-five years. Like all new methods it has been and is being abused. It will sink or rise eventually to its proper place in the general scheme. For the present and immediate future this book appears to reflect in proper proportion the best opinion on the subject.

H. GISSEL, Specialist for Surgery, and P. G. SCHMIDT, Specialist for Pulmonary Diseases: *Die Lungentuberkulose. With an introduction by* W. v. GAZA. *Pp. xiii + 192; Georg Thieme, Leipzig, 1933. Paper; R.M. 18.*

By MAX PINNER

The literature, particularly in Germany, is rich in books on pulmonary tuberculosis or some of its main aspects. It is therefore well justified to ask the *raison d'être* of each new book. The introduction by Prof. v. Gaza states that a particularly valuable piece of work was to be expected from the coöperation of a surgeon and a specialist in pulmonary disease. The authors themselves mention that this monograph is written particularly for the practitioner and the student. With these two guide-posts in mind the reviewer can find nothing to recommend this book. The whole subject is treated on 192 pages, including a good deal of illustrated matter. Of this space 51 pages are occupied by bacteriology, allergy and immunity, infection and pathological anatomy. The general manifestations of the disease, including symptomatology, laboratory examinations, physical signs and the various clinical aspects, occupy approximately 55 pages, while a total of 3 pages is devoted to extrapulmonary tuberculosis. Remembering the specific surgical qualifications of one author, one is astonished to find that the surgical treatment of pulmonary tuberculosis, including pneumothorax, is presented on 34 pages. The first nonclinical

chapters contain little that is not known by any practitioner, and they are hardly fundamental and certainly not reliable enough for the student. Throughout the book the impression is gained that it was written more by means of the scissors than by the pen. It hardly occurs that the authors relate personal experiences. The chapter on the prognosis of pulmonary tuberculosis and that on the results of surgical treatment consist entirely of quotations from other recent publications.

The publisher has done an excellent job of typography and reproductions.

M. ASCOLI AND M. LUCACER: *Simultaneous bilateral pneumothorax. With a preface by* F. DUMAREST. *Pp. 102 and 11 illustrations. Masson & Cie, Paris, 1932.* 22 francs.

By JOHN N. HAYES

Twenty years have passed since Ascoli and Faguioli first proposed and practised bilateral simultaneous immobilization of the diseased portions of tuberculous lungs by pneumothorax. Increasing knowledge of the physiology of respiration and improvements in technique and in the choice of subjects have resulted in a wider employment of this treatment in recent years. We have travelled far from Forlanini's ideas that the disease should be unilateral and that the lung should be completely collapsed and wholly immobilized. Ascoli has long held that simple relaxation, partial collapse, of the diseased portion of the lung is often successful and that total collapse may do harm (dissemination to the opposite side). He, therefore, proposed to combat the lesion with low but optimal intrapleural pressure. Various names have been applied to this method: "selective collapse," "relaxation, or small, pneumothorax." Having seen good results from this method in one-sided pneumothorax, Ascoli began to use it on both sides simultaneously.

Due to the reduction of the elasticity and of the distensibility of areas infiltrated with disease, air introduced into the pleural space comes to lie over them and favors their collapse, while the healthy parts of the lung continue to expand with inspiration (Morgan). Compensation through a delicate mechanism causes either no change or an increase in the ventilation of the lung, even when both have been partially collapsed and, therefore, not capable of normal distention. Vital capacity is not reduced in equal proportion to the amount of air introduced into the pleural cavity.

Pneumothorax affects the intrapleural pressure on the other side of the mediastinum and, in properly conducted bilateral pneumothorax, it is often possible to conserve the static and functional equilibrium of the mediastinum better than with unilateral compression. Various circulatory symptoms can be avoided by this means. However, the mechanism of compensation in

bilateral simultaneous pneumothorax is less prompt than with unilateral compression and, therefore, the patient should be observed closely (vital capacity, pulse and respiratory rates, blood-pressure, duration of voluntary apnoea).

The best indication for the method is the occurrence in the course of unilateral pneumothorax of an early or late spread of disease to the opposite lung, a common occurrence. If varying the degree of collapse of the original lung does not relieve the new condition, pneumothorax is indicated on the opposite side when serial stereoroentgenograms and other studies show that the disease is progressing. Less frequently both lungs are compressed from the beginning, especially in bilateral bronchopneumonic forms with a chronic or subacute course. Extensive lesions may be attacked cautiously if the vital capacity is above 1000 cc. (Liebermeister), but disease in the lower lobes is not favorable.

A less common indication occurs when the primary pneumothorax has been rendered ineffective by a mobile mediastinum, which may be restored to equilibrium by introducing gas on the opposite side. Sergent has employed double pneumothorax immediately after child-birth as a prophylaxis against the development of acute bronchopneumonic tuberculosis. It is interesting that in children better results are obtained than in adults. Intractable haemoptysis, when the first pneumothorax does not control it, may be stopped by bilateral compression.

The contraindications include disease in a patient in poor general condition, age above forty years, advanced laryngeal and intestinal tuberculosis, very toxic extensive, diffuse bilateral pulmonary tuberculosis, and large bilateral fibrous cavities, especially when they are situated near the periphery.

Technique varies with the individual patient. Special attention must be given to avoid anoxaemia. Some prefer to give the refills on the same day; others space them. The air should be inspired into the pleural cavity by its negative pressure and should not be injected. The needle should be relatively blunt and small amounts of air are usually recommended. The final pressure is negative or about atmospheric, but when adhesions prevent a good collapse it may be left positive. Stereoroentgenograms are required very frequently, even before and after each refill early in the treatment. Respiratory and cardiovascular symptoms of overpressure are usually easily controlled. Fortunately, pleural effusions are less frequent and are more benign than with unilateral pneumothorax, but pulmonary perforation is relatively frequent, though by no means always fatal. Diffusion of disease to the healthy parts of the partially collapsed lung is, however, more frequent than with unilateral collapse.

Duration of treatment varies. Practically, six to twelve months are often enough for the better lung. The more extensive disease of the opposite lung may be kept in repose longer.

One wishes that the authors had reported their own results of treatment. Considering the degree of involvement in the collected reports, 20 to 30 per cent of favorable results is very encouraging.

An appendix deals with primary contralateral pneumothorax of which Ascoli was the originator. When compression of the actively diseased lung is impossible on account of adhesions, pneumothorax on the opposite side will sometimes cause sufficient relaxation of the lesion to promote healing. When combined with phrenicectomy on the side of active disease, the results are even better. Some illustrative cases are reported.

Dumarest, in his admirable preface, endorses the authors' view that the treatment is exceptional and should be reserved to specialists in a sanatorium. He believes that phrenic-nerve operations limit its field and that, if the newer disease is of the localized fibrocavernous type, phrenicectomy or apicolysis should be chosen. As Dumarest says, this little book furnishes an indispensable guide to physicians who administer simultaneous bilateral pneumothorax.

HENRY LAURENS: *Physiological effects of radiant energy. With 80 tables and 104 figures in the text; pp. 610. American Chemical Society Monograph Series, Chemical Catalog Company, Inc., New York, 1933. Cloth; $5.00.*

By AARON EDWIN MARGULIS

Numerous as are books dealing with radiant energy and its biological effects, this reviewer turns to new ones with curiosity and expectation. The subject presents questions of great theoretical and practical interest. The physiologist as biologist notes that the catabolic animal world is immersed in a field of radiant energy just as surely as in an atmosphere of gases, and searches for significant adaptations and functional interrelationships other than the remarkable one of the retina and ciliary apparatus; and the conviction that motivates that endeavor may be compared to that of many biologists toward the question of the inheritance of acquired characteristics. The anabolic plant world is, of course, a vast storage-battery of solar energy. In the present generation the insight achieved into the mechanism of the partial dependence of normal bone development in early life on adequate amounts of the proper kind of radiant energy has been a conspicuous triumph and has intensified research. The physiologist as medical scientist also realizes that the rational use of radiant energy as a therapeutic weapon predicates exact physiological knowledge such as has not yet been adequately achieved.

But aside from these tangible considerations, the opportunity is presented to observe and speculate upon the interaction, not only of energy and matter, but also the focusing of two independent and unequally developed world views, the inorganic and the organic, upon a single problem, an interface resulting from a methodological dichotomy implicitly derived from Cartesian Dualism,

whose rationale may in this case prove questionable. To describe adequately the phenomena associated with the emission and absorption of energy by matter, there has grown up a theory consisting of a rigorous ordering of highly abstract ideas, which in their furthermost ramifications are rapidly becoming esoteric, as any one familiar with the wave mechanics of Schroedinger and its mathematical homologue, the matrix mechanics of Heisenberg, or the theory of Q numbers of Dirac, is aware,—the epistemological assumptions of which constitute the world view of the physicist. It has become trite, of late, to point out that biology is not only far from such inductive development, but that efforts toward a generally acceptable epistemological basis, whatever its form but at any rate logically necessary and methodologically sufficient, are relatively few. Now in the theoretical problem presented, for example, in the lethal effect of radiant energy on bacteria, there is an incompatability, not only between a certain density of energy and the persistence of some physicochemical structure, but also between the ensuing altered structure and that organization that we recognize as life. The uniqueness in this problem lies in the apparent succession in the ideological chain: absorbed energy → altered physical world picture → altered chemical world picture → altered biological world picture. We might note that from left to right the concept of organization (which may prove to be a primitive idea) assumes increasing importance. In reality, we have here three points of view toward, and three languages with which to discuss, a *single* event. And, in a search for a unistic theory by fusion of these separate ideologies, the biologist with monistic yearnings in his heart is presented with an opportunity to attempt a resolution of his dualism *necessitans*.

One would have thought therefore that the biologist approaching this fertile field of research (and this reviewer believes that the approach must be made in this direction) would have familiarized himself with at least the fundamentals of the tools to be utilized. But actually this was not so in so large a proportion of the cases that one cannot quarrel with the statement that much of the work done prior to 8–10 years ago is not tenable.

And so, in approaching books on the subject under discussion, one hopes for a discriminatory evaluation of the data and an orientation toward a monistic theory, both pertinent to the phthisiologist, who, as scientist or therapeutist, wishes to clarify his own restricted phase of the field.

In the preface to the *Physiological Effects of Radiant Energy*, Dr. Laurens, who is Professor of Physiology in the Tulane University School of Medicine and by his researches is closely identified with the subject, states that his aim was to compile a source-book, to which persons technically interested might resort, to obtain information on the main work that has been done in each phase, prompted by the conviction that the time is appropriate to review in detail the more outstanding evidences of the physiological effects of radiant

energy. This he accomplishes in a series of chapters of encyclopaedic scope on the effects of radiant energy on the skin, eye, circulatory system, blood, metabolism, body temperature, respiration, blood reaction, photodynamic sensitization, bacteria, toxins and antitoxins, proteins, and ferments. Although chiefly concerned with physiological effects, therapeutical considerations are not wholly avoided, and there are discussions of the effect on anaemias, resistance to infection, wounds and skin diseases, rickets, tetany, pellagra, and tuberculosis.

That Dr. Laurens saw fit to devote only two and one-half pages of the opening chapter to pertinent physical theory is praiseworthy. Persons who will turn to this book will undoubtedly not require such information, and the attempt to cover that enormous field briefly, such as most writers on this subject have attempted, usually results in a completely useless hodge-podge. We regret, however, that Dr. Laurens did include mention of the Rutherford-Bohr atom-model without stating that conceptual difficulties in utilizing this model, or indeed any model in systems more complex than the hydrogen atom, have practically led to its abandonment. His description of the physical methods to be employed in the two fundamental measurements of energy and its spectral distribution should give those readers not already familiar with them an excellent insight to the proper approach. In the remainder of this first chapter there is a most interesting compilation of the results of measurements of solar energy and its spectral limits accumulated by observers scattered all over the world. A careful study of these data is very instructive, as the variations are of greater degree than is commonly thought, the practical lesson of which to the heliotherapist is that the technique of insolation is very largely a local climatological problem.

The discussion of the effects of radiant energy on tuberculosis covers ground already familiar to phthisiologists and, since no original concepts or data are offered, detailed discussion is not warranted. The placing however, in juxtaposition, of the multitude of clinical opinions reimpresses one with the wide variation of clinical impression as to the efficacy of this therapeutic measure, in contrast to the more general agreement as to its contraindications. Phelps's work in attempting to implicate the 3200 Å–3800 Å band as the responsible one is given considerable space, and although his data, as Dr. Laurens points out, are not conclusive, this is rightly so, since it is one of the very few attempts to determine the portion of the electromagnetic spectrum significant for tuberculosis.

In a final chapter on the mode of action of radiant energy, recognizing the need of a unistic theory, Dr. Laurens, after reviewing the extant theories, such as the production of photodynamic substances, reflexes, formation of hydrogen peroxide, heating of blood, and absorbtion of split-protein products from irradiated areas, leans to the view that, granting that the incipient effect

is photoelectric, photochemical reactions ensue, and new or changed substances are produced, which, passing into the blood-stream, produce the variety of effects that have been described. If this be true, further advance toward a unistic theory will be conditioned by the advance of knowledge of the effects of radiation on chemical structure and reaction; and how difficult this subject is may be envisioned by the 31-page discussion of the changes involved in the activation of sterols.

Viewed as a whole, this book attains the high level of excellence that has come to be expected of *American Chemical Society Monographs*. The most serious criticism that might be made is that the utility and readability of this book might have been considerably enhanced by a greater synthesis and organization of the material presented, the lack of which is a common pitfall in directly incorporating a large amount of source material. One regrets also not to find that orientated, weighed appraisal of data that is almost obligatory upon anyone venturing to write a book,—that which distinguishes a discourse from an enumeration. That few conclusions are drawn is a reflection both of the state of the subject and the author's stated desire to do so except in obvious instances. Nevertheless, this book is an indispensable treatise to all interested in its field, and a leisurely study of it should prove of benefit to all those who would approach either the experimental study of, or the empirical use of, light in a scholarly fashion.

The typographical execution, the index, and the bibliography are quite satisfactory.

FRANK HAMMOND KRUSEN: *Light therapy. With frontispiece and 33 illustrations in the text. Pp. xx + 186. Paul B. Hoeber Inc., New York, 1933. Cloth; $3.50.*

By AARON EDWIN MARGULIS

Interest in the effect of sunlight on the healthy or sick organism dates almost from the dawn of recorded history, yet few empirical findings or theoretical notions have stood the test of time and rigorous critique. Nevertheless, use of light as a therapeutic agent has persisted with periodical enthusiasm. Particularly as regards tuberculosis, great interest lies in observing the vacillation of opinion. In rather marked contrast to the almost unbridled enthusiasm of the last decade is Sir Henry Gauvain's recent statement: "Let us be perfectly frank in the matter . . . . it is quite possible to cure any form of surgical tuberculosis without resort to light treatment . . . . [which] . . . . is not a specific but an aid. . . .", although a careful perusal of Dr. Wm. S. Halsted's early paper (1905) on the cure of nonpulmonary tuberculosis by noninterference and "open air" treatment might have quite early suggested that sunlight possibly does not play an all-important rôle in the routine of the helio-

therapist. However, radiant energy can most certainly reactivate tuberculous processes and there is as yet no satisfactory explanation of this phenomenon. The situation is very similar in most of the other diseases for which some form of light therapy, at the crest of its popularity, was recommended. The tendency of late has been to emphasize what light cannot do, in an effort to circumscribe its indications. The dominant need is for a convincing evaluation of its therapeutic effects and that is what one expects as justification for the appearance of a new book on the subject. Simultaneously one has some doubts whether this is as yet possible. The alternative is a mere recounting of an already oft-told tale.

Light Therapy, by Dr. Frank H. Krusen, director of Physical Medicine at Temple University School of Medicine, we note in the preface, represents such an attempt to epitomize the existing data to enable the physician who may read it to practise light therapy with ease and intelligence. And if, it is stated rather heroically, one physician is so instructed, the author will feel that the labor involved was not in vain!

Since a book of this type may conceivably reach a large audience of practitioners, and since it purports to orientate them and launch them upon a field already sufficiently bewildering, we shall examine its contents quite critically. For purposes of discussion the book may be arbitrarily divided into three parts.

The first, of five chapters, is an attempted exposition of the theoretical background, including definitions and history, physics, sources of therapeutic light, and physiology, all in 64 pages! The subject is presented mainly as a series of quotations selected more or less judiciously, a method open to serious objection as it breaks continuity and introduces unresolved contradictions. Especially annoying is the looseness of ideology, a fault especially to be avoided if brevity is not to be achieved at the expense of accuracy. It is certainly achieved at the expense of any possibility of real insight. Such brief presentations may lead to a verbal acquaintance with the ideas involved, but hardly more. We believe it an unwarranted assumption that the physician desiring to use light therapeutically would not be willing to apply himself more intensely. As examples of carelessness of ideology we might quote: (1) "Infrared therapy, the treatment of disease by . . . . that portion of the spectrum producing (*sic*) heat rays" (page 3). (2) "Visible rays have little if any proven physiological (*sic*) effect" [surely the well-known effect on the retina has had an enormous influence on the life of man] (page 12). (3) ". . . . merely to produce infrared rays it is necessary to heat the source to a temperature of from 100° to 400°" [all bodies above 0° Kelvin radiate in the infrared region] (page 13). In discussing filters the statement on page 53 that rock-salt filters out infrared radiation, when the reverse is true, is undoubtedly an unintentional error. The chapter on physiology is particularly weak, being a

series of quotations mostly in tabular form, without attempt at synthesis, and, since several are from publications many years old, errors of the past are repeated. The commendable features are the insistence and plea for knowledge of the exact effects of limited spectral regions and their antagonisms and synergisms; useful descriptions of the various types of generators available for therapeutic use and a table outlining their spectral limits, although graphs of their spectral distribution of energy, equally to the point, are not given. Rather astonishing is the omission of mention of the infrared in the mercury-arc spectrum, comprising some 60 per cent of the emitted energy, an omission which, so often not taken into consideration, abrogates in large part the experimental work done with this lamp.

The second part of our arbitrary division is an exposition of forms of administration of light therapy and the technique of administration, with which there is little quarrel. However, in the discussion of heliotherapy, no mention is made of the factors of latitude and altitude and season in conditioning the technique, without also mention of the possibilities of control by pyrheliometry for determination of total energy and spectography for determination of the lower spectral limit which varies with season for any location. Dosage is commendably outlined as largely an individual problem.

The main message of the book is contained in 13 chapters on the indications for and the proposed use of ultraviolet and infrared energy in systemic diseases. The plan followed is to list for each system the diseases in which each has been proposed, followed by an attempt, more or less weak, to crystallize out the truth from a commendably sceptical viewpoint. The general conclusion is reached that light therapy has been recommended in an absurdly large number of conditions, particularly dermatological, but that even after weeding, a sufficient number of undoubted therapeutic effects remain to indicate its great value. A short review of Dr. Krusen's attitude toward light therapy in tuberculosis only is in place here. He affirms its usefulness in most forms of nonpulmonary tuberculosis, particularly lymphatic, peritoneal, genitourinary, ocular, laryngeal, and bone-and-joint tuberculosis. Emphasis is laid on combined general and local irradiation. Less usual is his defense and advocacy of its utility in pulmonary tuberculosis, which point of view he has propounded elsewhere. His opinion is based on (1) the somewhat dubious argument that what is good for nonpulmonary tuberculosis must, *ipso facto*, be good for pulmonary tuberculosis—certainly a *non-sequitur*; (2) a personally favorable experience with 49 reported cases; and (3) a marshalling of corroborative bibliography, in large measure English, who in this reviewer's opinion are notoriously uncritical in the use of physical methods. He advocates its use as an adjunct to general measures except in toxic, advancing, active cases, and the use of sources low in infrared. Haemoptysis is considered an indication for caution and not discontinuance.

Chapters on contraindications, dangers, limitations, and a set of conclusions emphasizing the chaotic state of the subject, and repeating the most surely known facts, terminate the book.

To sum up in the light of its intentions, this book is a rather unsuccessful attempt at a manual of empirical usage. To one who seeks understanding of the fundamentals of the subject it might prove worse than worthless, although it pretends to cover the ground succinctly. To those who seek either convincing critical evaluation of effects or a list of instructions to hold in the left hand while turning a switch with the right, it will probably seem equally timid. Conceivably if the author had written the whole in his own words and, as Dr. Kolmer points out in his sympathetic introduction, given freer play to his own empirical experiences, surely of equal value to that of many of the authors he has so widely quoted, none of these criticisms might have been applicable.

Handbuch der Kindertuberkulose: Edited by PROF. DR. ST. ENGEL AND PROF. DR. CL. PIRQUET: *Vol. ii, with 170 partly colored illustrations, pp. x + 704. Leipzig, Georg Thieme, 1930. Paper; price for the 2 volumes, Mks. 160.*

By MAX PINNER

In reviewing the first volume of this handbook (see June, 1933), it was remarked that it showed a considerable lack of uniformity and that one misses a unity of spirit and purpose. In an explanatory note at the end of the second volume, the editors explain that it was their intention to produce, not the usual type of handbook, but to build it up out of independent monographic studies, leaving the single author completely free to decide on form and extent of his contribution. In other words what was critically remarked in the review of the first volume has apparently been the intention of the editors from the outset.

The second volume contains chapters on diagnosis, prognosis, prophylaxis and therapy; further, on epidemiological aspects, on tuberculosis in the various ages of childhood; a brief chapter on the tuberculosis in noninfected populations; on the relation between tuberculosis and constitutional factors and intercurrent diseases; a discussion of the present concepts of French authors on childhood tuberculosis and, finally, a brief chapter on childhood tuberculosis in America. Again, the choice of the contributors is excellent, in general, and the volume is a worthy companion for the first volume.

The physiological influences of different climates and the treatment of tuberculosis by climatic methods are discussed by 12 different authors, and this subject is allotted a considerable amount of space (129 pages). These chapters are quite disappointing. The general discussions on the physiology of

ocean climate and of the climate in high altitudes are vague, and certainly do not make use of all the data and definite facts which are available on this subject. Meteorological data are scanty and usually quite insufficient to be descriptive of the particular climate under discussion. When it comes to the question of climatotherapy, the reviewer finds that, after reading, with considerable interest, the ten contributions, he has learned to know the personal and strictly empirical opinions and experiences of ten different men but hardly any solid and well-founded facts. More or less all authors of this section make the *a priori* assumption that different climates exert definite physiological and therapeutical influences, but the evidence presented is so meagre as to convince nobody but the climotherapeutic enthusiast. This is not only due to the actual lack of knowledge of these relations, but even more so to the unsuccessful attempt at glossing over this lack by vague impressionistic statements and the continual use of such essentially meaningless terms as "mild climate," "stimulating climate," "pure air," "air with a high oxygen content," etc. Consequently, the indications for choosing a suitable climate for this or that type of patient rests entirely on empirical observations. Whatever few references are made to a physiological or therapeutical action of radiant energy are equally vague and empirical, if not incorrect.

The rest of the book, however, is replete with solid information, which is all the more assimilable because it is enlivened by the fairly strong subjective factors in the various contributions. It is to be regretted that its high price will probably prevent the wide distribution that this book deserves.

F. C. S. BRADBURY: *Causal factors in tuberculosis. National Association for the Prevention of Tuberculosis, Tavistock House North, London, 1933. Pp. x + 126. Paper; 2s.*

By BENSON BLOOM

The exceptionally high mortality from tuberculosis observed in the Tyneside area in England stimulated the National Association for the Prevention of Tuberculosis to have this study made, to determine, by medical and statistical means, the important secondary causes of tuberculosis in this region. This work, carried out by the author in an intensive manner for over a year, included the investigation of nearly 3,000 homes and of over 1,000 individuals or their medical records in the towns of Jarrow and Blaydon. No new concepts of tuberculosis are brought to light by this report, but it does begin to translate several of our loosely conceived ideas into terms of statistical accuracy. Numerous factors supposedly predisposing toward tuberculosis, such as poverty, undernourishment, overcrowding, poor ventilation, race, etc., were studied in detail; of these poverty was the only condition which showed a distinct sta-

tistical relationship to the frequency of the disease. The significant conclusion is reached that, although tuberculosis can obviously induce poverty, this is of relatively minor importance compared with the fact that poverty is definitely a cause of tuberculosis. Two sequelae of poverty, overcrowding and undernourishment, are of themselves considered to be factors in the high mortality rates in the towns studied, but statistical proof of this conclusion is not nearly as complete as is the case with the poverty factor. It is obviously an intricate task to separate statistically the closely interwoven factors involved in this study. This is especially true of the study of overcrowding, but by several different lines of reasoning the conclusion is reached that overcrowding is *per se* a significant element in the spread of tuberculosis. Here, as in the other studies, a causal relationship, and not simply an association, had to be determined; in this instance it was done by determining that overcrowding preceded the average date of onset of tuberculosis. It immediately becomes apparent that the data on which such statistical conclusions are reached are far from being mathematically accurate, dependent as they are on the human deficiencies of memory, judgment and opinion. The decision that overcrowding is an important contributory cause of tuberculosis in this region is at variance with some observations made on a much larger scale; for instance, in Germany at the end of the war-period the unusually high tuberculosis incidence was reduced when undernourishment was relieved at the same time that the striking overcrowding persisted, and, also, the excessive overcrowding in the east side of New York is associated with a low incidence of tuberculosis. Undernourishment is considered as a contributory cause of tuberculosis but probably only as secondary to the general condition, poverty, which produced it. Insanitation, more common in tuberculous than in nontuberculous families, was not proved to have a causal relationship to tuberculosis.

Many other interesting facts are elicited by this study. In the chapter on race, for example, it is shown clearly that part of the increased incidence of tuberculosis in Jarrow as compared with Blaydon was due to the greater proportion of Irish inhabitants of the former. The author inclined to the opinion that the increased incidence in the Irish in this community is due to some innate racial characteristic, but it seems more likely that other factors are at play, such as, for example, the more recent advent of country Irish people, as pointed out on page 61, to the crowded region of Jarrow. It was decided that maternity and child-welfare clinics played a definite rôle in decreasing the incidence of the disease, but the evidence for this is much less conclusive than one wishes. The excessive incidence of abdominal tuberculosis could not be explained on the basis of a bovine origin because of the small amount of milk intake (the astoundingly low figure of two-thirds of a pint per head per week) as well as because of the purity of the milk; the explanation lay, rather, in the

high incidence of pulmonary tuberculosis. The statement made in connection with the discussion of sanatorium treatment on page 87 that "the percentage of deaths was sensibly the same in those who had and those who had not sanatorium treatment" calls for a much more complete discussion.

This small volume is recommended to all who are interested in tuberculosis because it attempts to place on a sound statistical basis some generally accepted "notions" about the disease. Whether or not this attempt is successful may be questioned because of the small numbers involved but the method seems an excellent, though not necessarily the only, one for the problem; and it has been carried out in a most meticulous and thoughtful manner. No conclusions are drawn that are not warranted by the data exhibited. Similar studies in at least several other regions should be carried out to determine if the application of the method on a huge scale is justified.

G. S. WILSON: *Tuberculous bacillaemia. With appendices and notes by* HERTA SCHWABACHER, C. C. OKELL, AND E. A. WOOD. *Medical Research Council, Special Report Series no. 182. London, 1933, His Majesty's Stationery Office. Pp. 146; paper; 2s, 6d.*

By MAX PINNER

The problem of tuberculous bacillaemia has received a new impetus by Löwenstein's publications. This author has introduced new methods and has made quite unusual and astounding claims. Not only does he find tuberculous bacillaemia to be a very common occurrence in almost all phases of tuberculosis, but he claims this to be true for a number of diseases which have never been suspected to have anything to do with tuberculosis, such as rheumatic disease, various diseases of the central nervous system, etc.

Dr. Wilson's part of the present publication consists of 104 pages. It is a very timely and unusually exhaustive analysis of all the data available on the question of tuberculous bacillaemia. A large part is devoted to the work of Löwenstein and to those authors who have, usually in vain, tried to duplicate his results. Although Dr. Wilson's study is only a *Schreibtischarbeit*, it is of high value, particularly at the present time when Löwenstein's work is under such vivid and controversial discussion. The reviewer does not know of any contribution in which careful critical analysis has helped so much to illuminate this particular subject. Dr. Wilson comes to the conclusion that tuberculous bacillaemia is not a frequent occurrence, and that it does not exist in nontuberculous diseases unless they are complicated by gross tuberculous lesions. He believes that Löwenstein's excessively frequent positive results are due to "the failure to realize, or to pay adequate attention to, the numerous fallacies attending the demonstration of the tubercle bacillus." Among

these he mentions the occurrence in lysated blood of acid-fast particles, the failure to take precautions against a number of technical mistakes, the impossibility to distinguish the tubercle bacillus microscopically from other acid-fast bacilli of frequent occurrence, the assumption that macroscopical colonies of acid-fast bacilli are necessarily tubercle bacilli, and the assumption that acid-fast bacilli seen on smears from culture media are tubercle bacilli. The latter refers to the frequent reports of so called microscopical colonies of acid-fast bacilli, which refuse to grow on subcultures and which are not pathogenic for the usual laboratory animals. Further possible mistakes are pointed out in the diagnosis of inoculation tuberculosis in guinea pigs. Dr. Wilson adds a chapter on the description of the precautions that are necessary in practice for the unequivocal demonstration of the tubercle bacillus in infected material. It would be highly desirable that this chapter could somehow be made compulsory reading for all laboratory workers concerned with studies in tuberculosis.

In the first *Appendix* Herta Schwabacher reports her attempts to obtain blood cultures from 282 tuberculous and 122 nontuberculous patients. She followed in minute detail the technique which she was taught by Löwenstein in Vienna. She obtained 3 macroscopical cultures of tubercle bacilli of human type from patients with severe pulmonary tuberculosis; 2 microscopically positive cultures and 7 macroscopical cultures of chromogenic saprophytic acid-fast bacilli. She points out the frequency of the occurrence of acid-fast bacilli from the scrapings of cold-water taps. Another chapter by the same author is devoted to experimental bacillaemia in guinea pigs and rabbits. She found that in guinea pigs bacillaemia is a frequent phenomenon during advanced disease.

A third chapter of Miss Schwabacher relates the occurrence of saprophytic acid-fast bacilli in human and animal blood-cultures and their isolation from water, dust and comedones. The bacteriological characteristics of these bacilli are presented in great detail. They are all apathogenic for laboratory animals.

Dr. Wood tried to demonstrate the presence of tubercle bacilli in the blood of 23 patients with skin disease and in that of one normal person. For this purpose guinea pigs were inoculated successively, so that a total of 201 animals was used. In none of the animals was there any evidence of tuberculosis found. Eight of the patients were "cultured" according to Löwenstein's method and also gave negative results.

This monograph seems to the reviewer to be an unusually important and thorough study, both in its theoretical and critical, and in its experimental aspects. It may well be hoped that it will help greatly to solve some of the mysteries which seem to have been conjured by Löwenstein's publications.

ERNST MELZER: *Der Einfluss der Tuberkulose auf das Seelenleben des Kranken. With an introduction by* LUDGER RICKMANN. *Pp. xvi + 162. Ferdinand Enke Verlag, Stuttgart, 1933. Cloth; R. M. 6.60.*

By MAX PINNER

The literature is replete with papers and books dealing with the subject of the influence of tuberculosis on the patient's psyche. These publications vary all the way from semipolitical works to scientific efforts. They comprise books written in a Pollyanna style, as propaganda for a cheerful attitude of the patient, and other publications which specialize on the demonstration of how many brilliant persons have been the victims of the disease, but leaving out, as a rule, mention of the fact that the tubercle bacillus is totally impartial in regard to persons. The present volume represents an unusually thorough attempt at collecting and explaining observations relating to the psyche of tuberculous patients.

The author points out in the beginning that the psychological alterations in tuberculous patients are, in pathogenesis, of two different kinds: (1) the psychology of the patients is affected by the psychological experiences of the disease, particularly much so because it strikes so often in the prime of life when the patient may be full of ambitious plans; and (2), on the other hand, the psychology is influenced, indirectly as it were, by the physical-psychogenic hook-up chiefly *via* the vegetative nervous system. Dr. Melzer claims that the result of these two factors is a rather characteristic personality which he terms *tuberculous neurosis*.

In the first chapter the author discusses the strictly physical influences of the disease on the psyche of the patient. It is the impression of the reviewer that a good deal more evidence could have been presented in this chapter; but, as it stands, it is a sound basis for a more complete treatise on this one point. The rest of the book, with the exception of the last chapter, is devoted to the alterations which the disease as a psychological experience brings about. Here the author shows himself as a sensitive and well-balanced observer. Although some former statements may create the impression that he will present a definite and schematic personality in the tuberculous patient, this is not at all the case, because he first chooses the dynamic development from the early phases of the disease, with all that it may mean in disappointment, in isolation, and in some cases in relief from an all too difficult life. Furthermore, he depicts in a fascinating way the psychological reactions on the background of the premorbid personality. Greatly at variance with many other authors, he sees but little indication that the confinement, the isolation and the introversion that the disease enforces has any beneficial action upon the patient's psyche. Even in the most fortunate circumstances, psychological and physiological, he

believes that a readjustment of the patient is practically always necessary. He points out in particular how the disease is likely to warp the personality into egocentric and antisocial tendencies. The psychological development is further explained on the background of Adler's *Individual Psychology*. This is indeed an inviting experiment in observation, because the chronic tuberculous patient shows clearly all the requirements for the development, according to Adler, of a neurosis on the basis of a feeling of inadequacy on account of physical disease. An interesting but highly speculative part of one chapter shows the possible influences of "tuberculous psychology" on general political developments in a highly tuberculized country.

The last chapter gives some valuable indications of how psychotherapy may help some of the difficulties mentioned.

BRUNO HEYMANN: *Robert Koch. Teil 1, 1843–1882. With frontispiece, 12 illustrations and three facsimiles in the text. Pp. 353. Leipzig, 1932, Akademische Verlagsgesellschaft, M. B. H.; cloth.*

By AARON EDWIN MARGULIS

Fittingly appearing during the semicentennial year of Koch's announcement of his discovery of the tubercle bacillus, this latest biography of him gives promise to be the definitive one. So fascinating a theme as the life of Robert Koch has not been neglected. Four full length biographies[1] have been published, besides a large number of shorter sketches. But this full portrayal of his life and work that Professor Bruno Heymann of the University of Berlin contemplates in two volumes, of which only the above, the first, has appeared, easily surpasses that of his predecessors. Of the two principal ones, Dr. Karl Wezel's work, though lucid, was inadequately brief, and Dr. Hellmuth Unger's, though entertaining, was overromanticized. Dr. Heymann's treatment is thorough, reverential and fully sympathetic, yet dispassionate. With sufficient detail Koch's footsteps are traced in this first volume from birth to that momentous evening late in March, 1882, which Loeffler so truly labelled *ein Gedenktag in der Geschichte der Menschheit*,[2] when Koch rose to address the meeting of the Berlin Physiological Society to speak on the "Aetiology of Tuberculosis." Between these events are involved his formative student years, his work on the anthrax bacillus, the aetiology of wound infections and

[1] BECHER, W.: *Robert Koch, eine biographische Studie, Berlin, 1890, H. Conitzer's Verlag.* KIRCHNER, MARTIN: *Robert Koch, J. Springer, Wien & Berlin, 1924.* WEZEL, KARL: *Robert Koch, eine biographische Studie, Berlin, A. Hirschwald, 1912: Bibliothek Wm. Coler von Schjerning, vol. 36.* UNGER, HELLMUTH: *Helfer der Menschheit, der Lebensroman Robert Koch's, Leipzig, 1929.*

[2] LOEFFLER: *Zum 25=jährigen Gedenktage der Entdeckung des Tuberkelbacillus, Deutsch. med. Wchnschr., 1907, no. 13, p. 495.*

the pathogenic organisms, the methods for the isolation, cultivation, and photography of microörganisms, and his basic work in tuberculosis.

A graph of Koch's trajectory would appear like an autoöxidation curve, a crescendo gaining in momentum. Born in 1843, in 1866 he receives his doctorate in medicine at the University of Göttingen, where he had come under the influence of Jacob Henle the microscopist; in 1872 he establishes himself as a practising physician in Wollstein, where his scientific growth begins to accelerate; in 1876 he enters Ferdinand Cohn's laboratory in Breslau for that fateful interview in which he lays before the great botanist his work on the anthrax bacillus; in 1880 he is an associate of the *Kaiserliche Gesundheitsamt* in Berlin; in 1882 he announces the discovery of the tubercle bacillus and the monistic concept of tuberculosis, and the eyes of the world are focused upon him. We commend Professor Heymann for having included so much of Koch's correspondence in full. It adds greatly to the book. One achieves through reading it a very intimate insight into the rigorously self-critical ideals Koch consistently held before himself.

If there is any tendency to forget the scope of Koch's influence on medical science because of his popular association with tuberculosis, it will be counteracted in this biography. Koch was an indefatigable worker. His publications number almost two hundred. Besides his resolving of the chaos that was "bacteriology" before his advent, and his basic position as the pillar of modern bacteriology whose postulates of proof only of very late have been challenged, Koch cast his gigantic shadow upon public health, sanitation, experimental therapy and prophylaxis of infectious diseases, and stimulated Abbe's work on the microscope.

Since this biography appears as one of a series of *Studies of the Biology of Genius*, edited by Wilhelm Ostwald, it would seem that such inclusion is evidence of the recognition that Koch's life holds intrinsic interest other than the fact he was an eminent scientist. It is possibly true, as is often said, that the time becomes ripe for discoveries, that the stage is set, and that it remains for some individual equipped and adjusted to his *milieu* past, present and *future*, to accomplish his destiny by walking upon it. One wonders about and seeks for enlightment of such factors, extrinsic and intrinsic, that enabled Koch to thread his way through life as he did. There have been discussions as to whether he was a genius or not. It would be difficult, indeed, to draw fine distinctions between the enunciation of primitive ideas and the revelation of new interrelationships of such already enunciated: and far more difficult to differentiate on the basis of the proportionate compounding of these. The time might be ripe for discoveries, but there are degrees of ripeness, and the bridging of the step between the obvious and the not so obvious may vary in length, and in requisites of intellectual boldness and experimental skill. Certainly one does not feel in respect to Koch, as one assuredly does in respect to

Beethoven, for example, that crushing incapacity to understand the man in his entirety. One is astounded, but not bewildered. One does not sense a gigantic struggle with transcendental thoughts or emotions, but rather one is overwhelmed by the clarity with which, apparently, the goal is visualized and the directness and rapidity of the inner development. True, there was one period of groping (between 1866 and 1872), surely of great psychological importance. But, with one foot on the ladder, how rapid the climb!

But, indubitably, Koch might be called one of science's favored sons. Favored indeed was he with uncannily ingenious grasp of experimental difficulties, with prodigious powers of application; while one must not forget, the personal qualities, the convincing sincerity, and that aura that enabled him to tower over his too often jealous contemporaries by sheer weight, that gave Ferdinand Cohn, as he later confessed in a published letter,[3] instant appreciation of great potentiality and inner power. If we add that the problem, to which Koch felt within himself, consciously or unconsciously, the power to solve, represented something fundamentally vital to the existence of every living human being, one is staggered at the opportunities that life presented to a country doctor born of old Prussian stock, one of a family of 13 children living in the Harz. Of what moment then whether one calls him genius or no? What if perhaps he did appropriate more from others than he acknowledged? The problem was there. Koch solved it. Even his generation rewarded it.

One must commend the format and typography of the book, which is a distinctive addition to any library.

[3] COHN, F.: *Ein Brief über Koch, Deutsche Revue, 1 Quartal Band, Jährg. xvi, 1891.*

TUBERCULOSIS AMONG THE CHILDREN OF TUBERCULOUS PARENTS

A Statistical Study Following 136 Families into Adult Life[1]

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1. INTRODUCTION

If we knew which children were destined to develop in adult life the crippling or fatal form of pulmonary tuberculosis, a large part of the tuberculosis problem would be solved. This truism has always been realized, but the widespread work in case-finding now being carried on among school children, particularly in Philadelphia (14) (15) (20) (22) (23) (24), in Massachusetts (5) (6) (7) (4) (34), and in Chatauqua County (30) and Saranac Lake, New York, makes it seem possible that a partial answer to the question may be in sight. Since the childhood type of tuberculosis is comparatively seldom important of itself, the chief justification for such extensive work in schools is the belief that many of the future cases of adult tuberculosis will develop from present cases of the childhood type. This opinion is based on the facts that many cases of tuberculosis in young adults show signs of tracheobronchial lymph-node disease, and that, of the few cases that it has been possible to follow over a period of 5 or 6 years, a significant proportion of the positive childhood cases have developed adult tuberculosis. Kleinschmidt (18) has estimated from Rathbun's figures that a high-school child with childhood-type lesions is 27.5 times more likely to have adult-type lesions than one without childhood tuberculosis. Only time can prove the truth of this hypothesis: we cannot surely know till this generation of children has grown into adult life. Until that time, it is of great practical importance to use every means to find out if we are on the right track.

[1] This study was made possible by the Cambridge (Massachusetts) Tuberculosis and Health Association, upon whose records it is based. The authors are particularly grateful for the helpful encouragement of the President, Dr. Hilbert F. Day, and the Executive Secretary, Mrs. Mabel Greeley Smith. We wish also to acknowledge the invaluable help in locating families and in verifying records which we received from the Cambridge Board of Health and from many hospitals, social agencies and physicians of Cambridge and its vicinity. We are grateful to Dr. L. U. Gardner and Mr. D. E. Cummings of the Saranac Laboratory for their helpful suggestions and criticism.

Opie and Chadwick and their associates (4) (15) (22) (34) have shown conclusively that "contact" children (who are usually "family contacts") show a much higher proportion of demonstrable tuberculosis than do noncontacts. A recent article by Barclay (3) shows the children in 100 tuberculous families to be 23 per cent tuberculous. These findings are so thoroughly accepted that many case-finding campaigns in schools concentrate almost exclusively on the "contacts."

It occurred to us that a study following into adult life a group of children who had been exposed to tuberculous parents, and therefore had had a high percentage of childhood tuberculosis among them, would help us somewhat in answering the question: Which children are fated to develop adult tuberculosis? Pratt (29) reported in 1927 that only 2 of 88 children in the 44 families of tuberculous patients treated by his class method developed tuberculosis during a period of from 5 to 21 years. The available family statistics dealing with large numbers have been collected from the opposite point of view. They give us the family history of tuberculous individuals at the time they are patients, but they do not tell us what happens to the children of these people in after life. We do not know how many of these families grow up without clinical tuberculosis, never coming to the attention of the collector of statistics. We do not know how frequently the family occurs in which the children of a tuberculous parent succumb one after another to tuberculosis. Is it so common that, as some would have us believe, it practically holds the secret of the control of tuberculosis, or is it comparatively rare, remembered and magnified in importance because of its tragedy?

We present this report, realizing its inadequacy, especially because of the small number of families studied, and the comparatively short period of time which it covers, but with the hope that others will study their records from the same point of view. This simple method, applied to a large number of cases, would add to our knowledge of the epidemiology of tuberculosis, particularly of the relationship between the childhood and adult types of the disease.

2. MATERIAL AND PROCEDURE

The Cambridge Tuberculosis and Health Association, founded one year before the National Tuberculosis Association, has excellently-kept social records of more than 3,000 reported cases of tuberculosis in Cambridge who were under its care 1904–1915. Among these cases we

found about 600 cases of reported pulmonary tuberculosis in which the patient was a parent of children, one or more of whom were under 15 years of age when the case was reported. Many of these families we were of course unable to trace, and many of those which we did find were eliminated because the original diagnoses proved to be uncertain. The remaining 136 families (128 white and 8 negro) form the basis of this report. In 103 of these families there is a record in each instance of a positive sputum in the original case. In the other 33, we could find no records of sputum examinations, but the cases were typical in symptoms, were fatal, and were reported as deaths from tuberculosis.

In the great majority of instances we obtained information about the family by personal interview with one of its members. In a few instances we relied upon telephone conversations or correspondence with one of the family, or upon information received from an intimate friend of the family. Thanks to the friendly relationship existing between the Tuberculosis Association and these families, our questions were answered in a coöperative spirit, and, we felt sure, with no deliberate lies. Wrong causes of death we found were often given, when the real cause was tuberculosis, usually through ignorance, though sometimes undoubtedly from a fear of family stigma. However, it seems unlikely that, even in these families, we were misled in the mortality statistics by being told that dead individuals were living. The old records gave us excellent social histories of the families at the time they were known to the Tuberculosis Association, including the duration and degree of exposure to the disease. We obtained through our questions the subsequent history of each offspring, as to health, occupation and marital status, and, in case of death, the supposed cause, place and date of death. Except in cases in which tuberculosis was definitely known to be the cause of death, we looked up the official cause of death and were successful in finding it for every individual who died after the age of 4 years. Among the children, 0–4 years, there were 17 whose death certificates we were unable to find, and 9 others in that age-group in whom the official causes of death (for instance, "chronic bronchitis") were impossible to classify. Any conclusions from our material about this age-group are therefore impossible. Among individuals of 5 years and over, however, we feel that our mortality statistics are accurate. The official causes of death were definite and satisfactory with one exception. A white man, aged 33, who died a few hours after being brought to a hospital in coma, without a history, was recorded as dying from "chronic

endocarditis." There was neither X-ray examination nor autopsy. A record from another hospital showed him to have had chronic sputum-positive tuberculosis and a tuberculous ankle. We therefore felt it more accurate to list this case as death from tuberculosis. Morbidity statistics obtained merely by questions are of course only roughly approximate, but, by asking about the occupation and marital history of those reported as living and well, we felt that we gained a fair idea as to the presence of serious forms of tuberculosis.

All of these families, though varying somewhat in economic status, are of the industrial, wage-earning class, among whom the tuberculosis rate is known to be higher than in the general population. For example, the tuberculosis death-rate in the U. S. industrial population in 1922 was 114.2 per 100,000 (13) as compared to 97 per 100,000 in the U. S. Registration Area for that year (32). That the industrial population of Cambridge is no exception in this respect can be shown by a comparison of the tuberculosis death-rates in the different wards of the city 1922–1926 (table 1) (16).

TABLE 1

Death-rates from tuberculosis (all forms) per 100,000 living, by wards for Cambridge, Massachusetts, 1922–1926

WARD	1	2	3	4	5	6	7	8	9	10	11	TOTAL
White.....	67.4	111.2	113.7	113.2	98.3	100.5	61	52	50.3	44	81.4	80.2
Negro.....	0	0	75.5	359.5	201	293.8	225.5	232.5	73.5	49.8	153.5	229.2

Wards 8, 9 and 10, in which it will be seen that the death-rates were very low among whites, are largely made up of homes of the upper economic stratum of society, while the other wards are almost exclusively inhabited by the industrial population. Of the 136 families in this study, 66 lived, when first known, in wards 2, 3 and 4, where the death-rate is seen to be highest among the whites. Only 11 families lived in wards 8, 9 and 10, and none of these belongs to the upper economic class making up the bulk of the population of these 3 wards.

Of the 128 white families, 59 are of Irish stock, 26 English or American, and 19 are from Nova Scotia. Eight nationalities are represented in the other 24 families. We have no figures showing the racial distribution of the industrial population of Cambridge, though it is well known that the Irish predominate.

These families were followed through 1915 by the Cambridge Tubercu-

losis Association, whose staff of trained workers did everything in their power to lessen the danger of infection by removing the patient, where possible, and, where this was impossible, by training in hygiene and providing medical care. Often, too, material help was given, which improved the general nutrition of the families. But in those years, 1904–1915, there were few sanatoria, and those few were unpopular. Sixty patients were never removed from their homes, 64 were away less than a year (average 4.3 months), 9 were away for between 1 and 3 years, and 2 for 3 or more years. The remaining case was away from home for years and came home two months before death. All the cases were far advanced when reported, so that opportunities for heavy infection had already occurred. Coöperation from patients was also far more difficult to obtain in those days than now. Probably, therefore, the work of the Tuberculosis Association, though its importance in relieving suffering and in its broader educational aspects cannot be overestimated, was not able to reduce appreciably the number of cases of tuberculosis destined to develop later in these families. But this factor in possibly reducing the incidence of tuberculosis must be borne in mind in considering the tuberculosis rate in this group.

3. NEGRO FAMILIES

Tuberculosis in the Negro is known to be such a different problem from the same disease among whites that it seemed best to consider separately the 8 Negro families in this study. The number is too small to attempt any statistical conclusions. All we can be sure of is that these eight families have certainly not been spared from the ravages of tuberculosis. In these 8 families, there were 29 children, all born before or while the parent's case was known to be active. Seven of these have died of tuberculosis. One child, aged 4, died of "chronic bronchitis and exhaustion," which may have been tuberculosis. One girl, who later died of acute appendicitis, had had tuberculous cervical adenitis. Fifteen are now living and well, aged 21 to 41 years. The 8 known cases of tuberculosis occurred in 5 families (3 cases in 1 family and 2 in another) and the case of "chronic bronchitis and exhaustion" in a sixth family. Two families with 4 children were definitely without tuberculosis. All the families were thoroughly exposed. Of the two families definitely without tuberculosis among the children, one was classified as a "good" home, and one as "bad." Of the 5 families with

tuberculosis among the children, 4 lived in "good" homes, and one in a "bad" home.

4. WHITE FAMILIES

There were 128 white families in which one or both parents had pulmonary tuberculosis. Ninety-six had each a record of a positive sputum, and 32 were typical, fatal cases without records of sputum examinations. There were 563 children in these families. Thirty-seven of these children were born after their parents' tuberculosis was probably arrested, and one after his father's death from tuberculosis. These 38 children should not be grouped with those exposed to the disease; there were too few of them and they were born too recently to furnish material for conclusions. Eleven of them have died, all of causes definitely not tuberculosis, and the remaining 27 (ages 3–26 years) are living and well.

The remaining 525 children were born before or while the parent's tuberculosis was known to be active. Of these children 393 were under 15 years of age when the parent's case was reported. The fate of these 525 children is summarized in table 2.

TABLE 2

Fate of 525 white offspring exposed to tuberculous parents

	TOTAL NUMBER OF CHILDREN	DISAPPEARED	TOTAL DIED	DIED: CAUSES NOT TUBERCULOSIS	DIED: CAUSES UNCLASSIFIED	DIED: DEFINITE TUBERCULOSIS	DIED: MENINGITIS, PROBABLY TUBERCULOSIS	NON-FATAL TUBERCULOSIS
Under 5 years	525	0	67	35	25	6	1	0
Lived to 5 years and over	458	7	56	25	0	29	2	13
Living and known about in 1932:								
all ages	395							
Age-group:								
15–19	9							
20–24	67							
25–29	118							
30–34	101							
35–39	55							
40+	45							

It is evident that with 25 deaths, which cannot be classified, under 5 years of age, mortality statistics are impossible. Of those who lived to 5 years of age, the mortality figures are accurate, and since it is shown that those individuals living in 1932 have passed through part of the danger period, a study of their tuberculosis rate should give us some valuable information. The findings as to tuberculous morbidity are naturally only approximate, and undoubtedly underestimate the facts.

In table 3 are listed the important facts about the 31 fatal cases (including two cases of meningitis, organism not mentioned) and the 13 non-fatal cases of tuberculosis which occurred in those who lived till five years of age. For reasons given above we have not included the cases fatal before that age.

4A. COMPARISON OF THOSE FAMILIES WITH AND THOSE WITHOUT TUBERCULOSIS OCCURRING AMONG THE CHILDREN

Of the total 128 white families, 80 families, in which there were 275 children born before or while the parent's case was active, have shown no tuberculosis among the offspring up to the present. In 9 other families, with 49 children, there has been no definite tuberculosis, but there were children who died under 5 years of age of uncertain or unknown cause. The 51 cases of known tuberculosis (including the 3 cases of meningitis, organism not mentioned) occurred in 39 families with 201 children born before or while the parent's case was known to be active. Omitting the 9 families in which we cannot be sure whether or not some infants died of tuberculosis, let us compare the 80 families with no tuberculosis among the children with the 39 families in which definite tuberculosis occurred.

We find the age-level in the former group is slightly lower than in the latter. Those 80 tuberculosis-free families will undoubtedly be somewhat reduced in number before they reach the age-level of the other 39 families. However, this difference does not seem enough to be of major importance. If this artificial factor were removed, there would still remain a large number of families unscathed by tuberculosis.

Race: The English and American families fared slightly better than the Irish and Nova Scotians. Of the Irish families, 33.9 per cent had cases of tuberculosis among the children, as compared to 33.3 per cent of the Nova Scotian families and 22.7 per cent of the American and English families. The number of families of other racial stocks is too small to be significant.

Character of homes: Though all the families were of the wage-earning class, the social histories, written at the time the original cases were reported, enable us to classify the homes roughly in regard to living conditions and general care in matters of hygiene. We found that 40.4 per cent of the "bad" homes contained cases of tuberculosis among the children as compared to only 27.6 per cent of the "good" homes.

Source of infection: No significant difference was found in the incidence of tuberculosis among those exposed to the father or mother. It is interesting however that most of those children exposed under 5 years

TABLE 3

44 cases of tuberculosis in white offspring (5 years and over) of tuberculous parents of an industrial group (including 2 cases of meninigitis, organism not mentioned)

Fatal cases

FAMILY	SEX	POSITION IN FAMILY	FORM OF TUBERCULOSIS	AGE WHEN PARENT'S CASE REPORTED	AGE WHEN PARENT DIED	AGE AT DEATH FROM TUBERCULOSIS	PERIOD ILL PARENT WAS AWAY FROM HOME	EXPOSURE TO FATHER OR MOTHER	KIND OF HOME
A	M	2nd of 7	Pulmonary	10	10	22	0	Mother	"bad"
A	M	5th of 7	Pulmonary	5	5	17	0	Mother	"bad"
B	F	2nd of 8	Pulmonary	10	Parent still living	17	Few weeks	Father	"good"
B	M	3rd of 8	Pulmonary	8	Parent still living	32	Few weeks	Father	"good"
C	F	2nd of 10	Pulmonary	21	21	30	0	Mother	"good"
C	M	3rd of 10	Pulmonary	19	19	29	0	Mother	"good"
D	M	1st of 4	Pulmonary	13	14	20	0	Mother	"bad"
E	F	2nd of 5	Pulmonary	19	22	34	21 months	Mother	"bad"
E	F	5th of 5	Pulmonary	14	17	23	21 months	Mother	"bad"
F	F	5th of 12	Pulmonary	26 (Married and away from home)	Parent still living	28	0	Father	"bad"
F	F	10th of 12	Pulmonary	17	Parent still living	21	0	Father	"bad"
G	F	2nd of 3	Pulmonary	7 (Father) 12 (Mother)	8 (Father). Died before mother	19	6 months (Father) "off and on" (Mother)	Both	"bad"
H	M	1st of 6	Pulmonary	24	25	26	8 months	Father	"good"
H	F	3rd of 6	Pulmonary	19	20	22	8 months	Father	"good"
K	F	2nd of 3	Pulmonary	5	7	29	2 years, 9 months	Mother	"bad"
L	F	1st of 4	Pulmonary	Dead 3 years	Dead 3 years	24	Away for many years till 2 months before death	Father	"bad"

M	F	3rd of 7	Pulmonary	10	12	16	21 months	Father	"bad"
N	F	1st of 8	Pulmonary	23	23	27	0	Father	"bad"
O	M	2nd of 8	Pulmonary	13	13	29	3 weeks	Father	"bad"
P	F	1st of 2	Pulmonary	14	15	26	0	Father	"bad"
Q	M	3rd of 4	Pulmonary	11	13	33	Few weeks	Father	"bad"
R	M	1st of 6	Pulmonary	12 (Mother) 13 (Father)	13 (Mother). Died before father	23	0	Both	"bad"
S	M	1st of 5	Pulmonary	10	10	31	0	Mother	"good"
T	M	1st of 8	Pulmonary	21	27	33	1 year	Father	"good"
U	M	2nd of 8	Pulmonary	17 Away from home after father's case reported	20	30	9 months	Father	"bad"
V	M	3rd of 3	Pulmonary	12	18	26	0	Father	"bad"
W	F	1st of 2	Pulmonary	3	4	21	5 months	Mother	"good"
X	M	2nd of 3	Pulmonary	13	18	18	Few months	Mother	"good"
Y	M	1st of 5	Pulmonary	23	23	25	0	Father	"bad"
Z	F	1st of 6	Meningitis	Dead 20 years	Dead 23 years	5		Father	"good"
AA	F	6th of 7	Meningitis	5	Died before father	6	0	Father	"good"

Nonfatal cases

						AGE TUBERCULOSIS DIAGNOSED			
C*	M	7th of 10	Pulmonary, active	11	11	38	0	Mother	"good"
D	M	4th of 4	Lupus vulgaris	1	2	7 (Died of cancer at 24)	0	Mother	"bad"

TABLE 3—*Concluded*

FAMILY	SEX	POSITION IN FAMILY	FORM OF TUBERCULOSIS	AGE WHEN PARENT'S CASE REPORTED	AGE WHEN PARENT DIED	AGE TUBERCULOSIS DIAGNOSED	PERIOD ILL PARENT WAS AWAY FROM HOME	EXPOSURE TO FATHER OR MOTHER	KIND OF HOME
G	F	3rd of 3	Pulmonary, active	5 (Father) 10 (Mother)	6 (Father) 18 (Mother)	30	6 months (Father). "Off and on" (Mother)	Both	"bad"
I	F	4th of 5	Pulmonary, active	8	8	22	1 month	Mother	"good"
I	M	5th of 5	Pulmonary, active	4	4	19	1 month	Mother	"good"
J*	M	1st of 4	Pulmonary, active	5	5 (Father). Mother still living	27	0	Both	"bad"
BB	M	1st of 7	Pulmonary, arrested	11	Parent still living	15; well 24 years	0	Father	"bad"
CC	M	1st of 6	Pleurisy with effusion	5	Parent still living	15; well 17 years	2 months	Father	"good"
DD	M	2nd of 5	Hip	2	Parent still living	6	7 months	Father	"bad"
EE	F	2nd of 4	Hip	4	8 (Mother) 26 (Father)	Under 4	0	Both	"good"
FF	M	1st of 1	Shoulder	13	14	Some years later	2 months	Mother	"good"
GG	F	1st of 2	Cervical adenitis	9	10	9	0	Father	"good"
HH	F	3rd of 5	Cervical adenitis	Under 1 year	Under 1 year (Father) 7 (Mother)	17	0 (Father) 1 year (Mother)	Both	"good"

* Families C and J had also each a child under 5 who died of tuberculosis.

of age, who later developed tuberculosis, were exposed to the mother (see table 3). The children exposed to both parents were about twice as apt to develop tuberculosis as those exposed to only one.

Amount of infection: Every family except one was thoroughly exposed before the case was reported; many cases were not reported till just before or after death. The removal of the ill parent from the home after the case was reported had no apparent effect on the incidence of tuberculosis among the children. On the other hand, gross and inveterate carelessness in the disposal of sputum on the part of five patients did not seem to raise the tuberculosis rate among their children.

Time of exposure: It is impossible from our data to tell exactly when a child was first exposed. We know each child's age when the parent's case was reported, which is probably in most cases several years later than the beginning of the infectious period. Even allowing for this probability it will be seen from table 3 that exposure to tuberculosis in late childhood, as well as in very early life, may often be followed by later trouble. As is also shown in table 3, the greatest time elapsing between the reporting of the parents' disease and the death of a child from tuberculosis was 25 years, the least one year, and the average 11.6 years. Of the 7 cases of pulmonary tuberculosis among the offspring now living, the period between diagnosis of the parent's disease and of the child's varies from 4 to 27 years, averaging 18 years. In other words, many of these tuberculous offspring of tuberculous parents developed their disease years after they were first exposed, and often years after the death of the offending parent.

Families with two or more cases: In 29 families tuberculosis has occurred in only one child in each family. In the other ten families (see table 3, families A–J) occurred 22 cases, 43 per cent of the total known cases. In only one of these ten families (family C) were there more than two cases among the children. In general, we find in these ten families the same conditions somewhat intensified, as we found in the total 39 families with cases of tuberculosis among the children; that is, the proportion of "bad" to "good" homes is greater, and the proportion of Irish extraction is slightly greater. Double parental exposure is relatively just about as important as in the total 39 families.

4B. TUBERCULOSIS DEATH-RATES BY SEX AND AGE-GROUP

Though the number of individuals in each age-group is small, the number of years under consideration seems sufficient to make a calculation of death-rates worth while. Since there were very few of the younger groups living during the later years, and in the early years very

few of the older groups living, those years were omitted in which the small number living in that age-group did not warrant their inclusion in the calculation. However, as no year was omitted in which there was a death from tuberculosis, we did in several instances have to stretch the span of years under consideration further than was warranted by the number of individuals living. The irregularity in the periods considered is thus explained. This method seems probably to give results nearer the truth than if we had included the whole span of years or equal periods of time for each age-group. As a matter of fact, however, with either of these two latter methods, the variation in the figures would not have been enough to change their significance. The results are given in table 4 and in chart 1.

TABLE 4

Offspring of white tuberculous parents of an industrial group: death-rates from tuberculosis per 100,000 population by sex and age-groups, 1904–1931

YEARS	AGE-GROUP	MEAN NUMBER LIVING PER YEAR		TOTAL NUMBER OF TUBERCULOSIS DEATHS FOR WHOLE PERIOD		YEARLY DEATH-RATE PER 100,000	
		Male	Female	Male	Female	Male	Female
	years						
1895–1921 (females)							
1904–1921 (males)	*5–9*	*50.2*	*38.6*	*0.0*	*2*	*0.0*	*181**
1904–1921	6–10	51.7	45.2	0.0	1	0.0	110
1904–1921	8–12	53.1	47	0.0	0.0	0.0	0.0
1904–1926	*10–14*	*45.8*	*39.9*	*0.0*	*0.0*	*0.0*	*0.0*
1904–1926	11–15	46.2	41	1	0.0	93	0.0
1904–1926	13–17	46	41	2	2	187	195
1904–1932	*15–19*	*38.8*	*34.3*	*2*	*3*	*175*	*291*
1904–1932	16–20	38.2	34.4	2	3	178	290
1904–1932	18–22	37.8	34.0	2	4	180	411
1909–1932	*20–24*	*42.5*	*38.0*	*3*	*5*	*294*	*526*
1909–1932	21–25	40.5	36.8	3	5	308	543
1909–1932	23–27	36.1	33.1	4	4	459	483
1909–1932	*25–29*	*30.9*	*28.4*	*5*	*4*	*673*	*563*
1909–1932	26–30	28.1	26.0	5	5	740	769
1909–1932	28–32	21.8	21.2	5	3	954	566
1913–1932	*30–34*	*19.4*	*19.6*	*5*	*2*	*1288*	*510*
1920–1932	31–35	24.7	24.5	4	1	1242	310
1920–1932	33–37	18.5	18.5	2	1	827	410
1925–1932	*35–39*	*19.3*	*19.7*	*0.0*	*0.0*	*0.0*	*0.0*
1925–1932	36–40	16.6	17.6	0.0	0.0	0.0	0.0
1925–1932	38–42	11.7	14.0	0.0	0.0	0.0	0.0
1925–1932	*40 and over*	*9.0*	*14.0*	*0.0*	*0.0*	*0.0*	*0.0*

* Both the deaths in this age-group were from meninigitis, organism not mentioned. One (age 5) occurred in 1895, which made necessary the inclusion of the 10 years previous to 1904 in the calculations for the females of this age-group.

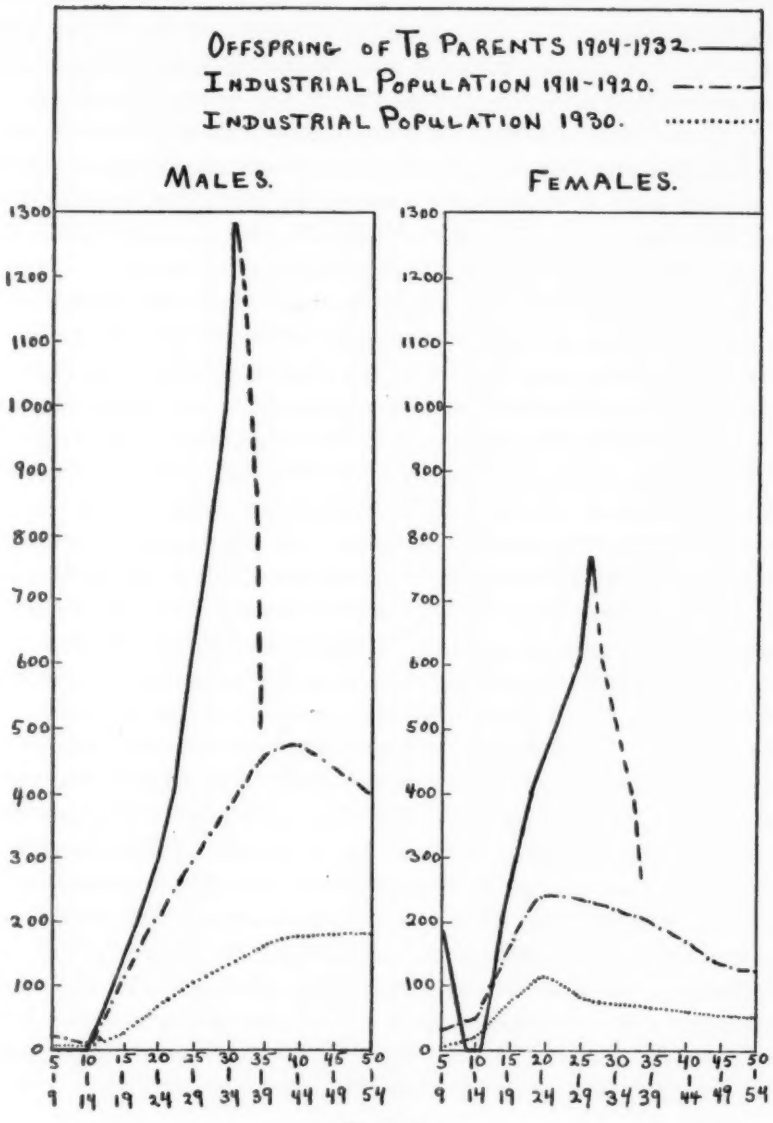

CHART 1

Death-rates for tuberculosis (all forms) per 100,000 living, by sex and age-groups. Offspring of white tuberculous parents in an industrial group 5–39 years of age, 1904–1932 (one death at 5 years in 1895), Cambridge, Mass. White industrial population from the Metropolitan Life Insurance Company, Industrial Department, 1911–1920, and 1930 (13) (20).

Since this study is of families of the industrial population, we have chosen for comparison in chart 1 curves compiled by the Metropolitan Life Insurance Co. from rates for their industrial policy holders (13). It is unfortunate that the periods of time in the two groups are not the same. If the years before and after 1911–1920 could have been included in the Metropolitan figures, the contrast between the two groups would undoubtedly have been even more striking, on account of the rapid drop in the tuberculosis mortality since 1920. The death-rates of the industrial population for 1930 are also indicated in chart 1 (21).

As it is, even if allowance is made for error due to the small number of individuals of tuberculous parentage, the difference between the death-rates of these two groups is enough to be significant. The ages from 7 to 13 are as free from tuberculosis in one group as in the other. In other words, these children exposed to tuberculous parents, if they lived to school-age, showed the same resistance to fatal tuberculosis as did their associates in school. At the age of 15 there is a sharp rise in the mortality curves in both groups. Also, in both groups the female curve rises more rapidly and reaches its peak sooner than the male curve, while the male peak is far higher than the female. But the differences between the two groups are more striking than the similarities. The male peak is reached ten years sooner in the group with tuberculous parents than in the general industrial population, and is almost three times as high. The female peak occurs at about the same age in each group, but is three times as high in the group with tuberculous parents. In this group, after the age of 30, the very small number of people living undoubtedly introduces an error. The sharpness of the drop in the curves at this age makes it seem probable that their general direction is correct, but the true curves, founded on large numbers of people, would certainly fall much more gradually. In summary, the male death-rate 15–39 years of age, 1904–1932, of those with tuberculous parents was a little more than twice as high, and the female rate a little more than $2\frac{1}{2}$ times as high as the rates for the corresponding groups in the general industrial population 1911–1920.

DISCUSSION

The small number of individuals considered in this study makes only tentative conclusions possible. Still, the increase in the tuberculosis death-rate during adult life among these children of the tuberculous seems striking enough to be significant.

It is unfortunate that our findings in the age-group 0–4 years are so unsatisfactory. However, since only a few years of following are needed, this age-group among children of the tuberculous has been thoroughly studied. Asserson's (1) (2) recent figures, though not extensive, are striking. Of 40 infants who remained with their tuberculous mothers, 26 died of tuberculosis, while, of 37 infants removed from their tuberculous mothers, only one died of tuberculosis. Jörgenson and Backer (17) followed 1,195 children born in Oslo, 1911–1925, in homes where there were open cases of tuberculosis. Ninety-two, or 7.7 per cent, died of tuberculosis before the end of the third year. Dow and Lloyd (11) found that, of 1,192 children born after a diagnosis of tuberculosis had been made in their parents, 1.3 per cent of those exposed died of tuberculosis during the first year of life, as compared to 0.58 per cent of those unexposed. Of 219 exposed children between one and five years old, two, or 0.91 per cent, died of tuberculosis, while of 126 unexposed children between one and five years old, one, or 0.79 per cent, died of tuberculosis. These writers quote Cox, who found that, among 1,486 children born in Lancashire 1919–1926, the death-rate of those exposed was far in excess of those not exposed to tuberculosis. Wahlquist and Myers (31), in following for two years a group of 71 children with a positive Pirquet test and family exposure, found a death-rate from tuberculosis of 8.4 per cent (6 cases).

These figures bear out the generally accepted impression that very young children exposed to a tuberculous parent are in more danger from tuberculosis than those not so situated. We can thus complete the mortality curve for such children from birth to about 39 years.

When we try to analyze the factors that have made these children of the tuberculous more susceptible to tuberculosis than a comparable group in the general population, and to discover why some have succumbed and others have remained in apparent health, we are on difficult ground. Some investigators (26) (27) emphasize the relative importance of inherited factors in determining the development of tuberculosis. The fact that Irish and Nova Scotian children among our families suffered slightly more than the American and English suggests the operation of constitutional factors though the difference is not striking enough to be of major importance. We could properly test the hereditary factor in our group of families only by comparison with another group of unexposed children of tuberculous parentage, or one of healthy parentage who were intimately exposed to the disease. From the data

quoted above for young children, it will be seen that such comparisons have been made which point to the greater importance of exposure over hereditary factors in causing fatal disease in this age-group. Intimate exposure in adult life, as shown by statistics of marital infection (8) (19) (25), is known to be of primary importance in causing serious disease. Reasoning by analogy, it seems likely that in our group of families long and close exposure rather than hereditary influence was the important factor in elevating the death-rate.

It is probably the duration and intimacy of the exposure that counts. For, though it is known that a single exposure may rarely result in disease, in general the mere fact of infection in childhood without long exposure does not seem to be dangerous. B. Lange (19) quotes Franz of Vienna and Ustvedt in Drontheim as finding no difference in morbidity or mortality from tuberculosis between groups of "tuberculin-positive" and "tuberculin-negative" children. He also quotes Frölich, who followed large groups of "tuberculin-positive" and "tuberculin-negative" 7-year-old children in Oslo till the age of twenty. There was a slightly greater morbidity rate in the "tuberculin-positive" group, but there was no difference between the two groups in the rates of serious morbidity and mortality from tuberculosis.

It is logical, as Lange advocates, to assume that the danger in prolonged and intimate exposure lies, not in "massive infection" which cannot be demonstrated as a possibility, but in the multiplied opportunities for infection to occur simultaneously with a temporary drop in the body's resistance, giving the bacillus a chance to gain a foothold. Children of grade-school age, even though heavily exposed, show high enough natural resistance to escape serious tuberculosis. The resistance of some of them, however, as we have found, may at times be sufficiently lowered to admit the establishment of a smouldering infection which, under the strain of puberty and early adult life, may burst into flame, often years after the removal of the source of infection.

Natural resistance, of course, covers many unknown factors, but is obviously affected by conditions of living, nutrition, work, etc. The findings among our industrial families show the influence of "bad" homes on the development of tuberculosis among those exposed. A similar study dealing with the offspring of tuberculous parents of a wealthier class would help further in determining the relative importance of economic circumstances and of close contact per se in causing tuberculous disease.

Difficult as it is to evaluate the fundamental reasons for our findings, the practical bearing of this study is more obvious. It is evidence against the theory that infection in childhood acts as adequate protective vaccination against disease in adult life (33). It lends support, on the contrary, to the work of Opie, Chadwick, Rathbun, and others, quoted above. If further studies with large numbers prove that such "contact" children really are destined to such a high tuberculosis death-rate in adult life, certainly we are justified in concentrating attention on these children, and, as a corollary, particularly on the children in whom the X-ray shows disease of the tracheobronchial lymph nodes. As long as 75 per cent of tuberculosis deaths occur within six months from the time the disease is reported, as they did in Massachusetts 1924–1929 (28), it is almost as idle as it was before 1915 to expect to accomplish much in preventing disease among the children of the tuberculous by breaking the contact or by instruction in sputum-hygiene. These measures should of course be attempted, remembering however that the damage has probably already been done. We must rely chiefly on measures supporting resistance and on periodic X-ray examinations for the early detection of progressive disease.

The results of this study also suggest that we beware of overemphasizing the danger to children of the tuberculous. Surveys which tell us of 25 per cent of tuberculosis among such children are probably misleading. Families riddled with tuberculosis we did not find very common, though they are important when they occur. Judging from the large number of children in our series who have grown up in apparent health, much of the tuberculosis found by clinical surveys may be of minor importance. Medical oversight of "contact" children is an important weapon, but it is only one of many in the complex fight against tuberculosis.

SUMMARY

The 592 children of parents with open pulmonary tuberculosis in 128 white families and 8 Negro families in the industrial population of Cambridge, Massachusetts, have been followed into adult life and a study made through questionnaires checked by official records of the tuberculosis-rate among them. Attention is given chiefly to the 554 children who were born before or while the parent's case was known to be active, and were therefore thoroughly exposed to the disease.

CONCLUSIONS

1. Tuberculosis mortality, 15–39 years, was at least between two and three times as high among offspring of white tuberculous parents in an industrial group as in the general white industrial population. The maximum number of cases among males occurred ten years earlier than in the general industrial population, while for females this maximum is approximately at the same age in the two groups. The age-group, 5–14 years, was as free from tuberculosis in one group as in the other.

2. Children in families of English and American stock were found to be very slightly less subject to tuberculosis than those of Irish or Nova Scotian stock.

3. "Bad" homes and double parental exposure seemed to be important in causing tuberculosis among these children. Removal of the ill parent from the home, carelessness in sputum disposal and whether exposure was to father or mother seemed to be of no importance.

4. Many of the children who developed tuberculosis in adult life were first exposed in late childhood. Often many years elapsed between the time of known exposure and the development of disease.

5. About two-thirds of the families of white tuberculous parentage have grown up without, so far, any known case of tuberculosis among the children.

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A FURTHER STUDY OF TUBERCULOSIS IN PUBLIC-SCHOOL CHILDREN[1,2]

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A study (1) of public-school children in Philadelphia has been continued in order to confirm previous observations on the incidence among them of tuberculous infection as shown by the tuberculin test and of various tuberculous lesions as shown by X-ray examination. It was also hoped that this study would throw light upon prophylactic measures suitable for children with potentially serious lesions, that might be adopted within the school system. Further evidence obtained in regard to the significance of various lesions found in the earlier survey is reported elsewhere (2).

Results of investigations into the incidence of tuberculous infection and of tuberculous lesions in children in various parts of the United States have recently been published. Unfortunately, the diverse methods employed render comparisons somewhat speculative. The selection of children for examination varies considerably in this and in other countries. For example, Hamburger and Monti (3), among the older workers, examined children convalescent from contagious diseases in a hospital; Barchetti (4), Sander (5), and Dickey and Seitz (6) examined children attending dispensaries, and Garrison (7), children in institutions. The majority of examiners have chosen school-children. Even with these there may be some unavoidable selection because permission for examination must usually be obtained. Hamburger (8) questions the use of dispensary children in determining the incidence of tuberculous infection among children because a large proportion are sick. On the other hand, Dickey and Seitz (6) believe that the use of dispensary children permits the determination of an approximate mean of tuberculous infection of children, including both sick and well, whereas the sick are presumably excluded from the school population.

It is now generally recognized that the cutaneous scarification tuber-

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Aided by a grant from the Metropolitan Life Insurance Company of New York.

culin test is less accurate than the intracutaneous test, yet the Pirquet method continues to be employed. This is doubtless partly through habit, partly for ease of application and partly because it is said to be less objectionable to parents and children. Even when the intracutaneous test is adopted, the quantities of tuberculin injected often vary in different surveys, so that results are not comparable. In school surveys in Ontario (9) only one injection of 0.05 mgm. of Old Tuberculin was made. Harrington and Myers (10) employed a maximum injection of one minim of a 1 to 100 solution, and Dickey and Seitz (6), 0.1 mgm.; whereas most observers, for example, Barnard, Amberson and Loew (11), Doolittle (12), Korns (13), Aronson (14), and Leggett and Callahan (15), gave a final injection of 1.0 mgm. of Old Tuberculin. However, even when the quantities of tuberculin and the route of injection have been the same, variations in the potency of the tuberculin used, as well as differences in the interpretation of reactions, doubtless have played a part in producing results that are not comparable.

Comparisons of the results of X-ray examinations in different investigations into the incidence of tuberculous lesions are also difficult. The fluoroscope was used in the examination of school-children by Keiffer (16); in examining university students it was used by Kattentidt (17), and in part by Soper and Wilson (18). It has been little used in this country because radiographic examination is considered more accurate. This usually consists of stereoscopic or single films of the chest in the posteroanterior position. Sometimes an oblique view is taken. Confusion arises through differences in technique, faulty interpretation of films, and the lack of clearly defined terminology. The report of Hawes and Friedman (19), recording wide variations of opinion in a group of six observers who examined roentgenograms of the chests of 109 children, shows that special training and valid criteria are requisite for the correct interpretation of chest films.

INCIDENCE OF INFECTION SHOWN BY TUBERCULIN TEST

The methods used in the application of the tuberculin test and the interpretation of X-ray films in our investigation of the incidence of tuberculosis in the school-children of Philadelphia have been described (1) (20). Additional tuberculin tests made upon children in two schools have been added to the 4,107 tests already reported and are shown in table 1. The additional tests confirm the conclusion that the incidence of tuberculous infection in Philadelphia is high. At the age of 15 years,

704 children were tested with tuberculin and 566, or 80.4 per cent, reacted. Barnard, Amberson and Loew (11) report that in New York 67.3 per cent of 1,000 children between the ages of 12 and 15 reacted to

TABLE 1

Tuberculin tests of 5,443 school-children of Philadelphia grouped by age, sex and race

Age in years	WHITE						COLORED					
	Boys			Girls			Boys			Girls		
	Number tested	Positive		Number tested	Positive		Number tested	Positive		Number tested	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent		Number	Per cent
3	0	0		0	0		3	2		2	0	
4	4	1		7	4		6	5		8	2	
5	30	11	36.6	42	23	54.7	23	5	21.7	28	16	57.1
6	64	39	60.9	61	31	50.8	37	12	32.4	47	29	61.7
7	69	39	56.5	76	46	60.5	68	36	52.9	63	36	57.1
8	81	50	61.7	109	81	74.3	92	58	63.0	89	56	62.9
9	75	41	54.6	59	40	67.7	90	60	66.7	96	71	73.9
10	72	58	80.5	105	79	75.2	65	49	75.4	105	73	69.5
11	77	62	80.5	74	46	62.1	83	67	80.7	103	84	81.5
12	97	75	77.3	87	70	80.4	89	69	77.5	98	79	80.6
13	131	87	66.4	110	93	84.5	92	84	91.3	107	85	79.4
14	200	141	70.5	178	147	82.6	72	67	93.1	92	77	83.7
15	343	269	78.4	238	193	81.1	59	52	88.1	64	52	81.2
16	372	297	79.9	286	258	90.2	23	20	86.9	27	24	88.9
17	221	172	77.8	178	162	91.0	13	11		11	11	
18	105	90	85.7	66	61	92.4	3	3		7	7	
19	40	32	80.0	9	9		1	1		1	1	
20	9	8		0	0		0	0		1	1	
Total.....	1,990	1,472		1,685	1,343		819	601		949	704	
In 5-year age-groups												
3–4	4	1		7	4		9	7		10	2	
5–9	319	180	56.4	347	221	63.7	310	171	55.1	323	208	61.3
10–14	577	423	73.3	554	435	78.5	401	336	83.7	505	398	78.8
15–19	1,081	860	79.6	777	683	87.9	99	87	87.9	110	95	86.4
20	9	8		0	0		0	0		1	1	
Total.....	1,990	1,472		1,685	1,343		819	601		949	704	

1.0 mgm. of tuberculin. They suggest that the preponderance of Italian children in their group may have lowered the percentage of reactors. Doolittle (12) tested 1,437 high-school students in Honolulu, of whom 75.6 per cent reacted to 1.0 mgm. or less of Old Tuberculin. Observa-

tions in Kingston, Jamaica, show a similarly high incidence of tuberculin reactions (21). It may be noted that the results obtained in both these widely separated cities, as in Philadelphia, are similar to those reported years ago in Vienna (3). These tests were performed in a manner similar to ours, and suggest that the true percentage of reactors among city children is higher than is usually reported.

We have noted no significant difference in the percentage of reactors attributable to sex and race. The percentage of white girls who reacted is somewhat higher than the percentage of white boys, but it differs very little from the percentage of colored boys and girls who had positive reactions. Other observers have found that boys react more frequently than girls of the same ages. Aronson (14), in a survey of rural communities of the South, found reactions in 10 per cent more colored than white children. Several observers have pointed out that the number of persons who react to tuberculin depends chiefly or solely on opportunity for infection. Other factors, however, such as age, sex and race, may play a part in the susceptibility to progressive disease or may modify opportunities for infection.

INCIDENCE OF LESIONS AS SHOWN BY X-RAY EXAMINATION

The results of X-ray examinations of all the children examined in both surveys are shown in table 2, with the exception of School A, previously reported (20), which has been omitted because only a small number of children were examined by X-ray. The additional examinations reported here include 633 pupils from school H, 677 from school J, 1,314 from school K, and 890 from school L. In the last two schools in the present study X-ray examination was made without the preliminary tuberculin test. In the first two, X-ray examination was given to all children, with few exceptions, who reacted to 1.0 mgm. or less of Old Tuberculin. As already shown (20), the occurrence of pulmonary or lymph-node lesions of tuberculous origin is very infrequent in children who fail to react to 1.0 mgm. of tuberculin. In all parts of table 2 discrepancies between the numbers tested with tuberculin and the numbers given roentgenological examination represent mainly the children who did not react to tuberculin.

We believe that percentages of lesions based upon the number of children tested with tuberculin rather than upon the number examined by X-ray, when negative reactors are excluded, gives a fairly accurate conception of the incidence of tuberculous lesions in presumably healthy

school-children. X-ray examination alone was given in the second survey of schools K and L in order to test the effect of omitting the tuberculin test in obtaining the consent of parents and pupils to examination.

In all four schools X-ray examinations consisted of stereoscopic anteroposterior views, but no oblique or rotated views were taken as in most of the schools in the former survey. When two lesions were found in one person only the more important lesion is listed in table 2.

The significance of the types of lesions may be discussed briefly. Calcified lesions of the lungs or tracheobronchial lymph nodes usually indicate heavy initial exposure to tubercle bacilli (22). These lesions are probably not in themselves a source of danger to the child (2), but Opie (23) has pointed out that, with partially calcified nodes, there may be progressive tuberculosis in other lymph nodes or in the pulmonary parenchyma. Caseous lymph nodes, sufficiently large to be demonstrated in X-ray films, represent a large tuberculous focus without evidence of healing. Lesions of this type have grave significance until calcification has occurred. Latent nonapical tuberculous infiltration of the lung may be roentgenographically soft and unstable in appearance, and from this lesion manifest pulmonary tuberculosis of the childhood type may develop. The majority of such lesions, however, when first seen are strand-like and have no clinical significance. Latent apical tuberculosis in adolescence, since it is recently acquired, is always a serious lesion. Manifest tuberculosis, however trivial the symptoms or physical signs, requires treatment (see also reference 24).

Table 3 shows the percentages of various tuberculous lesions found in white and colored children. Two age-groups are shown, the dividing line being approximately the beginning of puberty.

Calcified foci in the lungs or lymph nodes were found with approximately equal frequency in boys and girls and in white and colored children. In children from 15 to 19 years of age they occurred in 16.3 per cent of white boys, 18.7 per cent of white girls, 20.8 per cent of colored boys, and 17.1 per cent of colored girls. Caseous lesions of the tracheobronchial lymph nodes without demonstrable associated tuberculous lesions occurred in two colored and three white girls. They are included with the calcified lesions because their number is small.

Tuberculous lesions regarded as significant occurred, in the age-group from 5 to 11 years of age, in 0.2 per cent of white boys (manifest tuberculosis) and in 0.4 per cent of white girls (0.2 per cent latent apical tuberculosis and, excluding strand-like lesions, 0.2 per cent soft, latent

TABLE 2A

Results of roentgenological examinations of 5,798 white school-children in Philadelphia

Age in years	BOYS							GIRLS						
	Number examined	Number examined by X-ray	Number with pulmonary nodules	Number with calcified foci in tracheo-bronchial nodes	Number with latent childhood type infiltration	Number with latent apical tuberculosis	Number with manifest tuberculosis	Number examined	Number examined by X-ray	Number with pulmonary nodules	Number with calcified foci in tracheo-bronchial nodes	Number with latent childhood type infiltration	Number with latent apical tuberculosis	Number with manifest tuberculosis
4	4	0	0	0	0	0	0	7	4	0	1	0	0	0
5	30	4	0	0	0	0	0	42	11	1	0	0	0	0
6	64	25	0	2	0	0	1	61	17	1	1	0	0	0
7	69	17	1	2	1	0	0	76	29	3	2	0	0	0
8	81	32	2	2	1	0	0	109	54	4	9	2	0	0
9	75	28	4	3	0	0	0	59	30	1	3	0	0	0
10	72	45	1	5	1	0	0	105	70	6	6	1	1	0
11	77	67	4	7	0	0	0	74	58	4	6	0	0	0
12	102	83	5	11	0	0	0	103	86	16	10	0	0	1
13	161	120	8	12	1	2	0	208	190	11	27	0	1	0
14	337	279	11	29	2	3	2	454	418	26	38	6	1	2
15	583	497	20	65	7	3	1	622	576	28	64	9	9	4
16	611	528	29	73	7	8	0	598	569	36	81	7	9	2
17	360	310	10	45	8	1	1	329	312	17	58	5	13	4
18	169	154	8	29	3	0	0	89	83	10	10	5	2	3
19	46	38	3	7	1	1	1	11	11	1	3	1	0	0
20	10	9	0	0	0	0	0	0	0	0	0	0	0	0
Total...	2,851	2,236	106	292	32	18	6	2,947	2,518	165	319	36	36	16
In 5-year age-groups														
4	4	0	0	0	0	0	0	7	4	0	1	0	0	0
5– 9	319	106	7	9	2	0	1	347	141	10	15	2	0	0
10–14	749	594	29	64	4	5	2	944	822	63	87	7	3	3
15–19	1,769	1,527	70	219	26	13	3	1,649	1,551	92	216	27	33	13
20	10	9	0	0	0	0	0	0	0	0	0	0	0	0
Total...	2,851	2,236	106	292	32	18	6	2,947	2,518	165	319	36	36	16

TABLE 2B

Results of roentgenological examinations of 741 colored school-children in Philadelphia

	BOYS							GIRLS						
Age in years	Number examined	Number examined by X-ray	Number with pulmonary nodules	Number with calcified foci in tracheobronchial nodes	Number with latent childhood type infiltration	Number with latent apical tuberculosis	Number with manifest tuberculosis	Number examined	Number examined by X-ray	Number with pulmonary nodules	Number with calcified foci in tracheobronchial nodes	Number with latent childhood type infiltration	Number with latent apical tuberculosis	Number with manifest tuberculosis
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	2	2	0	0	0	0	0	1	0	0	0	0	0	0
5	12	3	0	0	0	0	0	12	6	1	0	0	0	0
6	12	5	0	0	0	0	1	20	14	1	1	0	0	0
7	30	15	0	0	2	0	0	32	15	0	0	1	0	0
8	31	15	1	0	1	0	1	39	18	0	1	1	0	1
9	37	19	0	1	0	0	2	36	19	0	3	0	0	0
10	10	6	0	2	0	0	0	36	19	0	4	0	0	0
11	25	17	0	3	0	0	0	30	21	0	0	0	0	1
12	27	12	0	1	0	0	0	39	28	2	3	1	0	1
13	28	23	1	0	0	0	0	36	25	1	2	1	1	0
14	22	19	1	4	0	0	0	43	33	8	1	0	0	0
15	26	20	2	2	0	0	0	35	28	1	3	1	0	0
16	29	26	2	3	0	0	0	32	30	0	2	0	1	0
17	18	16	0	4	1	0	0	22	22	1	6	0	1	1
18	7	6	1	2	0	0	0	9	9	2	2	0	0	1
19	1	1	0	1	0	0	0	1	1	0	0	0	0	0
20	0	0	0	0	0	0	0	1	1	0	0	0	0	0
Total...	317	205	8	23	4	0	4	424	289	17	28	5	3	5
In 5-year age-groups														
3– 4	2	2	0	0	0	0	0	1	0	0	0	0	0	0
5– 9	122	57	1	1	3	0	4	139	72	2	5	2	0	1
10–14	112	77	2	10	0	0	0	184	126	11	10	2	1	2
15–19	81	69	5	12	1	0	0	99	90	4	13	1	2	2
20	0	0	0	0	0	0	0	1	1	0	0	0	0	0
Total...	317	205	8	23	4	0	4	424	289	17	28	5	3	5

tuberculous infiltration of childhood type), in 3.7 per cent of colored boys (2.5 per cent manifest tuberculosis and 1.2 per cent soft latent tuberculous infiltration of childhood type), and in 1.5 per cent of colored girls (1.0 per cent manifest tuberculosis and 0.5 per cent soft latent tuberculous infiltration of childhood type). No significant lesions were found in colored boys 12 to 19 years of age but of the colored girls in this age-group 2.8 per cent had significant lesions (1.4 per cent manifest and 1.4 per cent latent apical tuberculosis). In the higher age-group there were a few pupils more than 18 years of age. In white boys 12 to 20 years old lesions regarded as significant were found in 1.0 per cent (0.2

TABLE 3

The incidence of various tuberculous lesions in white and colored school-children

AGE 5–11 YEARS	NUMBER OF CHILDREN EXAMINED	NUMBER OF CHILDREN EXAMINED BY X-RAY	PER CENT WITH PULMONARY NODULES	PER CENT WITH LESIONS OF TRACHEO-BRONCHIAL NODES	PER CENT WITH LATENT CHILDHOOD TYPE INFILTRATIONS	PER CENT WITH LATENT APICAL TUBERCULOSIS	PER CENT WITH MANIFEST TUBERCULOSIS
White boys.....	472	218	2.5	4.4	0.6	0	0.2
White girls.....	533	273	3.7	5.3	0.6	0.2	0
Colored boys...	159	82	0.6	3.8	1.9	0	2.5
Colored girls...	206	112	1.0	4.4	1.0	0	1.0
AGE 12–20 YEARS							
White boys.....	2,379	2,018	3.9	11.4	1.2	0.8	0.2
White girls.....	2,414	2,245	6.0	12.1	1.4	1.5	0.7
Colored boys...	158	123	4.4	10.8	0.6	0	0
Colored girls...	218	177	6.9	8.7	1.4	1.4	1.4

per cent manifest and 0.8 per cent latent apical tuberculosis), and in white girls similar lesions were found much more frequently, namely, in 2.3 per cent (0.7 per cent manifest tuberculosis, 1.5 per cent latent apical tuberculosis, and 0.1 per cent soft latent tuberculous infiltration of childhood type).

The white children examined in our survey were mainly first-generation Americans, in large part of Jewish and Italian stock. The economic status of the families of these children has probably been poor, although families who were able to send their children to high-school may be assumed to be somewhat more affluent than their neighbors. The number of significant lesions in elementary school-children below the age of 12 was small, probably about 0.3 per cent. On the other hand, significant lesions were found in 1.0 per cent of white boys 12 to 20 years

of age and in 2.3 per cent of white girls. We have become increasingly convinced that preventive work is more needed in the adolescent group than among younger children.

However colored children in the younger group have shown a high incidence of significant lesions, namely, approximately five times as much as white children. In the older group the number of colored children examined was too small to be comparable with the number of white children.

FACTORS INFLUENCING CONSENT TO EXAMINATION IN SCHOOL SURVEYS, AND PROBABLE VALUE OF RESULTS OBTAINED

The tuberculin test was omitted in two schools, K and L, in order to determine how great a part objection to the test plays in the reluctance of parents and pupils to consent to examination. In school L, previously surveyed and reported (20) as school "E," little difference was noted; out of a school population of about 2,500 pupils, 890 reported for examination in 1931, as compared with 722 in 1928. However, between the two surveys new teaching officials had replaced the old and little if any influence was used to persuade pupils to take the second examination.

The results were more significant in school K. Since about 90 per cent of 527 girls had reacted to tuberculin when previously tested in this school, designated in the former report as school "F," the time saved by omitting the test compensated to a large extent for the additional cost of films of the children who presumably were negative to tuberculin at our present examination. Three years earlier only 28.3 per cent of the students reported for tuberculin test and X-ray examination, but in 1931 the parents of 1,125 girls, slightly more than 58 per cent, consented to X-ray examination of the lungs. There had been no noteworthy change in the staff of the school, and the principal and teachers took a keen interest in persuading the girls to be examined. Apparently dislike of the tuberculin test deters many high-school pupils from submitting to examination.

Consent to examination may be refused for various other reasons. Some parents may think examination unnecessary because their children are apparently healthy. Those who consult their family physicians are often confirmed in this view. School surveys have, indeed, been criticized on the ground that the healthy do not come to examination, and that the incidence of tuberculous lesions found in those examined is therefore too high to represent the school as a whole. However, we

have more than once found parents highly indignant when told that their children have tuberculous lesions; such people apparently have agreed to the examination to confirm their own opinion that their children are in excellent health.

On the other hand, some parents and children may withhold consent because they fear the possible discovery of serious disease. Two girls in school K, who had been found three years previously to have latent nonapical tuberculosis of the lung, refused to undergo reëxamination because the earlier examination had caused them to worry about their health. Some workers believe that this attitude is so prevalent that the incidence of lesions found is too low to correspond with that actually existing in the entire school population. But again our interviews with parents have shown that many send their children to be examined

TABLE 4

Results of examinations at different dates in school K‡

DATE	NUMBER EXAMINED	PER CENT OF TOTAL PUPILS	PER CENT WITH CALCIFIED FOCI IN LUNGS OR LYMPH NODES	PER CENT WITH LATENT CHILDHOOD TYPE INFILTRATION	PER CENT WITH LATENT APICAL TUBERCULOSIS	PER CENT WITH MANIFEST TUBERCULOSIS
1928	527*	28+	22.3	1.5	1.1	1.5
1931	1125†	58+	16.7	1.1	1.5	0.8

* By tuberculin test and X-ray.
† By X-ray alone.
‡ Reported in 1929 as school F.

because they are in poor health or because of known contact with tuberculosis. These and other motives may tend to balance each other in influencing the results obtained, although statistics cannot be collected in support of this possibility. The fact that our second survey confirms the results of the first tends to support it, since it seems unlikely that any one of the motives suggested is constantly operative.

Comparison of the percentages of pupils in school K in whom various lesions were found in 1928 by X-ray examination preceded by the tuberculin test, and in 1931 by X-ray examination alone, is shown in table 4.

It is probable that the percentage of calcified foci in lungs and lymph nodes was smaller in 1931 than in 1928 because in the second survey, unlike the first, no oblique films were taken and no attempt was made to verify suspected lesions of this nature that were not definite on one examination. The percentages of children with latent tuberculous

infiltration of childhood and of adult type varied only between 1.1 and 1.5 per cent. A wider variation was observed in the percentage of clinically manifest tuberculosis found, being 1.5 per cent in 1928 and 0.8 per cent in 1931.

It is significant that the percentage of cases of clinical tuberculosis in the first survey, when 28+ per cent of the pupils were examined, is about twice as large as the percentage in the second survey, when 58+ per cent of the pupils consented to examination, the actual number of cases found in both being approximately the same, namely 8 in 1928, and 9 in 1931. When obvious ill health exists, parents and pupils apparently consent more readily to medical examination. Exceptions are known to occur, as in one school in which several months after a survey was made a boy who refused examination had a haemorrhage in the school yard, was found to have far-advanced tuberculosis of the lungs with a large cavity, and died a few weeks later. Nevertheless, it is probable that, even when only part of a school is examined, all or almost all of the pupils with manifest lesions may be included. On the other hand, nearly identical percentages of latent infiltrations of both childhood and adult type were discovered in the two unequal groups of school children. These figures suggest that the percentage of latent lesions of various descriptions found in part of a school population is fairly representative of the whole school, but that the percentage of clinical tuberculosis is greater than it would be if all the pupils were examined.

Thus it appears that it may be possible to find all the cases of manifest tuberculosis in a school when pupils voluntarily present themselves for examination, but that only part of the latent lesions that threaten health will be discovered.

PROPHYLACTIC CONTROL WITHIN THE SCHOOL SYSTEM

The principal and the teaching staff of school K coöperated with us in an effort to establish suitable measures within the school for the control of serious latent lesions. A rest-room was set aside for girls with such lesions. They were advised to eat adequate lunches and to decrease home work. Restricted physical exercise has taken the form of modified gymnasium and other activities. Parents of these pupils were interviewed concerning prophylactic care at home and the opportunity to have reëxaminations at intervals of three months was offered to them. During the summer holidays several pupils with more advanced latent lesions were sent to a preventorium.

Nevertheless, we do not feel hopeful that it is possible at present to provide adequate prophylactic care in this or in similar schools. The only space available for a rest-room was a wide corridor, which could easily accommodate four beds but could not be shut off because it was used by crippled pupils to reach the only elevator in the building. The possibility of suitable rest-room facilities awaits further building operations. Adequate supervision of the child's home routine would require the services of a school nurse working in close connection with the physician, which would entail added expense to the school medical service. Modification of the curriculum by diminishing the number of classes and lengthening the course, although advocated, did not seem feasible.

Another difficulty in establishing prophylactic measures lies in the constant migration of pupils in the school system of a large city like Philadelphia. More than one-third of the girls selected as needing preventive treatment for tuberculosis left the school when the term ended in January, 1931. Since apical lesions are more numerous in older girls, the need for prophylactic care usually arises within two or three terms of graduation, when the time for treatment is short and when pupils are especially reluctant to take it.

We believe that the numerous tuberculous lesions that were found in school K could be controlled if the difficulties due to overcrowding, pressure of school work and lack of nursing service were overcome. Principals in other high-schools have taken only a superficial interest in the results of our examinations.

We had also hoped to obtain further information about other measures for controlling tuberculosis in the schools. Little is definitely known about the value of preventoria and open-air schools in the treatment of latent tuberculous lesions. Their influence on the progress of disease can be determined only by prolonged investigation requiring:

1: The care in considerable numbers of children with various types of tuberculous lesions that threaten to undermine health.
2: Continued observation of these children while under treatment.
3: Persistent follow-up visiting to ascertain the ultimate result of treatment.
4: Comparison with control groups of the same economic status who have not attended open-air schools or preventoria.

Our examinations during the past five years of pupils in open-air classes connected with the school system have not given the desired

insight into their value. These Nutrition Tuberculosis Classes as at present conducted have been an unfavorable field for observation. The number of pupils attending was small; they had been admitted without adequate examination, and most of them were found to have no significant tuberculous lesions (25). We have had little knowledge of the home circumstances of the children. Changes in the class are so frequent that a considerable number of pupils are under observation for only a short time, partly because of the natural ambition of the older children to be transferred to regular grades where they advance more rapidly in their studies. Most of the lesions found were calcified foci of the tracheobronchial lymph nodes, which do not in themselves make children especially liable to the subsequent development of tuberculosis. All the children leave the classes before adolescence, when the incidence of manifest disease increases and the latent apical lesions appear, from which develops the greater part of the tuberculosis of early adult life. No follow-up work is done to obtain information concerning the pupils during these age-periods, which would throw light upon the effectiveness of the preventive care afforded by open-air classes.

Long-continued observations of a considerable number of cases can alone determine the effect of an altered regimen that tends to prevent mental and bodily fatigue. It seems probable that such measures will influence favorably latent apical lesions, if precautions are also taken to guard against further infection. Adolescent children with more extensive latent apical tuberculosis, latent childhood-type infiltrations that are not strand-like, and manifest pulmonary tuberculosis, however trivial the symptoms or physical signs, should be sent to a sanatorium or should have rest in bed, with careful supervision, including periodic X-ray examinations until the films show a strand-like lesion (24) (26).

RESULTS OF THE EXAMINATIONS IN THE VARIOUS SCHOOLS

More detailed results of the examinations in the respective schools are given in the following pages, together with protocols from one school, in which especially interesting cases were found.

School H: This elementary school, with children in grades from first to eighth, was chosen for further study because of its similarity to School D (20) already reported. School H was a well-lighted, well-ventilated modern school, having 892 pupils, half of whom were colored. The school was situated in a district thickly populated by people in very poor

circumstances. The parents of 633 children (70.9 per cent) consented to the examination. The results of tuberculin tests are shown in tables 5 and 5A.

TABLE 5

Tuberculin tests of children of school H grouped by age*

AGE IN YEARS	BOYS			GIRLS			TOTAL		
	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive
White									
4	0	0		3	2		3	2	
5– 9	116	83	71.6	100	87	87.0	216	170	78.7
10–14	98	85	86.7	72	63	87.5	170	148	87.1
15–17	3	3		2	2		5	5	
Total.....	217	171		177	154		394	325	
Colored									
4	2	2		1	0		3	2	
5– 9	64	41	64.1	73	55	75.3	137	96	70.1
10–14	40	35	87.5	55	50	90.9	95	85	89.5
15–17	2	2		2	2		4	4	
Total.....	108	80		131	107		239	187	
White and colored children									
4	2	2		4	2		6	4	
5– 9	180	124	68.9	173	142	82.1	353	266	75.3
10–14	138	120	87.0	127	113	89.0	265	233	87.9
15–17	5	5		4	4		9	9	
Total.....	325	251		308	261		633	512	

* With 0.01 mgm., 0.1 mgm. and 1.0 mgm. of O.T.

TABLE 5A

Comparison of reactions to tuberculin in school D and school H

	POSITIVE				NEGATIVE		TOTAL NUMBER TESTED WITH TUBERCULIN
	To 0.01 mgm. O.T.		To 0.1 and 1.0 mgm. O.T.		To 1.0 mgm. O.T.		
	Number	Per cent	Number	Per cent	Number	Per cent	
School D.....	209	38.1	102	18.6	237	43.2	548
School H.....	242	38.2	270	42.6	121	19.1	633

Comparison of the results of examinations in the two schools shows that the incidence of infection indicated by the tuberculin test is higher in school H than in school D, in which, however, the greater number of serious tuberculous lesions were found by X-ray. In school D 43.5 per cent of the children in the age-group 5 to 9 reacted to tuberculin, and in school H, 75.3 per cent; in the age-group 10 to 14 years, 63.2 per cent reacted in school D, and 87.9 per cent in school H. However, it is seen from table 5A that this increase in the total number of positive reactors was confined almost entirely to those reacting to the larger quantity of tuberculin. On the other hand, 339 children, or 61.9 per cent, of the children in school D, and 391, or 61.8 per cent, of the children in school H, failed to react to 0.01 mgm. of tuberculin; 209, or 38.1 per cent, of the children in school D, and 242, or 38.2 per cent, of the children in school H, reacted to 0.01 mgm. of tuberculin. It has been pointed out (reference (20), table 23) that tuberculous lesions occur with much greater frequency among children who react to the smaller quantity of tuberculin than among those who do not react or react only to the larger quantities.

The reason for the number of reactors to the larger amounts of tuberculin found in this school is obscure. The method of administering the test was the same in both surveys. The death-rate from tuberculosis for the two-year period from April 1, 1929, to April 1, 1931, in the area from which school D actually draws pupils was 284.3 per 100,000 and in the area from which school H draws pupils, 219.4. In school D more children may have come from households with open tuberculosis. This probability is supported by the greater number of serious tuberculous lesions found among them. It is conceivable that the high percentage of tuberculin-positive children found in school H might be explained by an undetected case of tuberculosis spreading tubercle bacilli about the school, although evidence pointing to this means of dissemination was not found. Decisive information could be obtained by compulsory examination of the entire school, including all the pupils, teachers and personnel.

The incidence of tuberculous infection demonstrated by the tuberculin tests increased with the average age of the pupils, and in the higher grades was 80 per cent or more. Of the lower grades the class in one room had a notably high percentage of reactors, namely, 87.8 per cent. However, of the 36 children who were positive to tuberculin, 24 reacted only to the larger quantity. In this room one child had clinical tubercu-

losis, but tubercle bacilli were not found in the sputum. Two had calcified lesions of the tracheobronchial lymph nodes.

In table 6 are shown the results of roentgenological examination of children in school H who reacted to 1.0 mgm. of tuberculin.

Of 243 pupils examined in school D, 25 had pulmonary nodules, 11 latent pulmonary infiltrations, 35 tuberculosis of tracheobronchial lymph nodes, none had latent apical lesions, and 5 had clinically manifest disease. However, results of roentgenological examination in the

TABLE 6

X-ray examination of children in school H grouped by age

AGES	NUMBER EXAMINED	WITH PULMONARY NODULE	WITH LATENT PULMONARY INFILTRATION	WITH TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES	WITH LATENT APICAL TUBERCULOSIS	WITH CLINICALLY MANIFEST TUBERCULOSIS
4	4	0	0	1	0	0
5– 9	261	3	3	11 (2)	0	3
10–14	226	4	1	24 (2)	1	1
15–17	8	0	0	2 (1)	1	0
Total in School H.....	499	7	4*	38†	2‡	4§

* Tuberculous infiltration of the lung was accompanied by recognizable lesions of tracheobronchial lymph nodes in 1 case.

† Tuberculosis of tracheobronchial lymph nodes accompanied by latent pulmonary infiltration, latent apical, or manifest tuberculosis is indicated in parentheses and, being listed in corresponding columns, is not included in the total.

‡ Latent apical tuberculosis was accompanied by recognizable lesions of tracheobronchial lymph nodes in one case.

§ Manifest tuberculosis was accompanied by recognizable lesions of tracheobronchial lymph nodes in 3 cases.

two schools are not exactly comparable. In school D four films were made—an anteroposterior stereoscopic pair and rotation and oblique exposures (20); in school H, the rotated view was not taken. This omission is probably largely responsible for the discrepancy between the percentage of children in the two schools in whom pulmonary nodules were demonstrated, since it is often difficult to differentiate blood-vessels and nodules without the aid of a film taken in the rotated position (24). These lesions have been shown to be of no clinical significance.

Again in school D children under 10 years of age were not given X-ray examination unless they reacted to 0.01 mgm. of Old Tuberculin, but in school H 163 children under 10 years of age who reacted only to 0.1 mgm.

or 1.0 mgm. of tuberculin were included. In this group 161 children were found to be normal on X-ray examination, one child had a pulmonary nodule and another a calcified lesion of a tracheobronchial lymph node. If these children were omitted from table 6, the results of examination made in school D would be closer to those in school H.

TABLE 7

Tuberculin tests of white children in school J grouped by age and sex

	BOYS			GIRLS			TOTAL		
Age-group	Number tested	Number positive	Per cent	Number tested	Number positive	Per cent	Number tested	Number positive	Per cent
12–14	17	13	76.4	26	20	76.9	43	33	76.7
15–19	364	292	80.2	249	223	89.6	613	515	84.0
20	2	1		0	0		2	1	
Total.....	383	306		275	243		658	549	

Results of X-ray examination of children in school J grouped by age

AGE-GROUP	NUMBER EXAMINED	WITH PULMONARY NODULE	WITH TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES	WITH PULMONARY INFILTRATION	WITH LATENT APICAL TUBERCULOSIS
12–14	31	3	1	0	0
15–19	521	24	65 (4)*	10 (3)†	14 (1)‡
20	2	0	0	0	0
Total.....	554	27	66	10	14

* When tracheobronchial lymph-node lesions have accompanied pulmonary infiltration or latent apical tuberculosis they are listed under these headings and are here indicated in the parentheses but are not included in the total.

† In three instances tuberculous pulmonary infiltration was accompanied by recognizable lesions of tracheobronchial lymph nodes.

‡ In one instance latent apical tuberculosis was accompanied by recognizable lesions of tracheobronchial lymph nodes.

It should also be noted that the average age of children tested with tuberculin in school D was 10.7 years, but that the average age in school H was 9.3 years.

School J: School J is a high-school for girls and boys situated in a mixed residential and industrial district. Approximately three thousand pupils are housed in a well-lighted modern school building. The financial status of the residents of the district is probably somewhat higher than in the district from which school G (20) takes pupils and it is decidedly

higher than the district from which schools E and F take pupils (20). In school J, 677 children (23 per cent) were given tuberculin tests. Of this number 8 were colored boys in the age-group 15 to 19, and of these 7 reacted to tuberculin; 10 were colored girls in the same age-group, 8 of whom reacted to tuberculin. In addition, one colored girl 20 years of age had a positive reaction.

The results of the tuberculin tests of 658 white children are shown in table 7. The percentage of pupils who react to tuberculin is about the same as in schools E, F, and G, already reported, being 80.2 for white boys in the age-group 15 to 19 years and 89.6 for white girls in the same age-group.

The results of roentgenological examination are shown in table 8. No instance of manifest tuberculosis was found in the school. Of the

TABLE 8

Results of X-ray examination of children in school K grouped by age

AGES	NUMBER EXAMINED	WITH PULMONARY NODULE	WITH TUBERCULOSIS OF TRACHEO-BRONCHIAL LYMPH NODES	WITH LATENT PULMONARY INFILTRATION	WITH LATENT APICAL TUBERCULOSIS	WITH MANIFEST TUBERCULOSIS
12 to 14	277	14	31	2	0	1
15 to 19	848	45	99	10	17	8
Total.....	1,125	59	130	12	17	9

total number of children tested with tuberculin 14, or 2.1 per cent, had latent apical tuberculosis, and 10, or 1.5 per cent, had latent tuberculous infiltration of childhood type. Latent apical tuberculosis was found in 9, or 3.1 per cent, of 286 girls who were tested with tuberculin, and in 5, or 1.3 per cent, of 391 boys. Several of the latent apical lesions were of slight extent and in no case did apical infiltration extend below the clavicle. The incidence of advanced lesions was in marked contrast to previous observations in schools F and G. The better economic status of the district may have promoted control of tuberculous lesions through better food-supply and living conditions, and they may have been further controlled by early diagnosis and removal of clinically tuberculous children from the school.

School K: The total results of X-ray examinations obtained in 1931 in this high school for girls, reported here as school K, and obtained in

1928 in the same school, reported as school F, have been compared and discussed (table 4, p. 151). The following table shows the incidence of the various lesions found in the second survey among the 1,128 girls examined, grouped according to age.

At our second examination four girls (K, 1 to 4) had pulmonary tuberculosis that could be readily diagnosed by symptoms and physical signs alone, and five others (K, 5 to 9) had apical lesions that had caused symptoms or physical signs. Latent apical tuberculosis was found in 17 girls (K, 10 to 26) and latent tuberculous infiltration of childhood type in 12 girls. Of the whole number examined, 0.8 per cent had manifest tuberculosis; 1.5 per cent, latent apical tuberculosis; and 1.1

TABLE 9

Results of X-ray examinations of children in school L grouped by age

AGES	NUMBER EXAMINED	WITH PULMONARY NODULE	WITH TUBERCULOSIS OF TRACHEO-BRONCHIAL LYMPH NODES	WITH LATENT PULMONARY INFILTRATION	WITH LATENT APICAL TUBERCULOSIS	WITH MANIFEST TUBERCULOSIS
12–14	177	6	10	0	1	0
15–19	713	26	92	6	3	1
Total.....	890	32	102	6	4	1

per cent, latent childhood-type infiltrations. The case histories of the first two groups are given at the end of the paper and are illustrated in the plates.

School L: School L is the same high-school for boys whose pupils had been examined three and one-half years before and reported as school E. In the present survey X-ray examination was given but the tuberculin test was omitted, as in school K. Of an average of 2,500 pupils attending this school, 722 were examined in 1928, and 890 in 1931. During the interval between examinations a new principal was placed in charge of the school and little attempt was made to persuade pupils to take the examination.

Since approximately 74 per cent of pupils previously examined reacted to tuberculin about one-quarter of those examined in the present survey were presumably negative to tuberculin, and, as regards the discovery of tuberculous lesions, X-ray examinations given to the tuberculin-negative children in this group may be regarded as wasted effort.

In table 9 are shown the results of the second examination of the boys of this school, grouped according to age.

Thirty-two pupils, or 3.6 per cent, had calcified pulmonary nodules and 102, or 11.4 per cent, had calcified lesions of the tracheobronchial lymph nodes. This number is somewhat lower than at the previous examination, probably because films in the oblique position were not taken and no effort was made to confirm the presence of lesions of this type if they were not unquestionably present at the first examination. One student, or 0.1 per cent, had manifest pulmonary tuberculosis; four, or 0.4 per cent, had latent apical tuberculosis; and 6, or 0.7 per cent, had pulmonary infiltrations of the childhood type, which in 4 boys consisted of old strands.

SUMMARY

Additional tuberculin tests in two schools in Philadelphia confirm the high incidence of tuberculous infection previously reported. In the age-groups 15 to 19 years, 79.6 per cent of white boys, 87.9 per cent of white girls, 87.9 per cent of colored boys and 86.4 per cent of colored girls reacted to tuberculin.

The incidence of tuberculous lesions that threaten to undermine health was approximately 0.3 per cent in white children 5 to 11 years of age, and more than five times as frequent in colored children of the same ages.

The incidence of serious tuberculous lesions in children 12 to 20 years of age was 1.0 per cent for white boys and 2.3 per cent for white girls.

In school surveys based upon consent of parents and pupils to examination, the percentages of latent lesions obtained are probably representative of the entire school population, but the percentage of manifest tuberculosis is probably higher than it would be if the whole school were examined, apparently because of a greater willingness of pupils and parents to consent to examination when tuberculosis has disturbed health.

Under the conditions of our survey the tuberculin test unfortunately deters many people from giving consent to examination. When determination of the incidence of infection is not considered essential the tuberculin test may be omitted, in order to survey larger numbers of school children. Some of the children given X-ray and physical examinations will presumably be tuberculin-negative, but this waste may be compensated for by saving the cost of a general application of the tuber-

culin test to groups presumably in large part tuberculin-positive. School administration and health officers with the aid of parents might devise a plan by which all children could be fully examined.

The need of prophylactic care for school-children with significant latent lesions is not generally recognized. The value of treatment in open-air classes and preventoria can be determined only by long-continued observation of large groups of children, with accurate diagnoses and adequate controls. Conditions in the schools reported here have not made possible the collection of information concerning the value of prophylactic care within the school system. Nevertheless, it is reasonable to suppose that measures of established value in arresting clinical tuberculosis will prevent the development of latent into clinical disease, if adequately applied to appropriate subjects.

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PLATE I

School K (High-School for Girls)

K1: Girl, Italian, aged 14 years. Weight, 90 per cent of normal for age and height. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* On the left there was dense soft infiltration in the lateral half of the apex extending as low as the 5th rib with less dense infiltratlon in the 5th interspace. There was scanty infiltration above the clavicle and moderately dense infiltration as low as the 7th rib on the right side. On physical examination there was limitation of movement and diminished resonance over the upper half of the right lung anteriorly with coarse dry râles over this area. On the left there was diminished resonance over the upper half of the lung both anteriorly and posteriorly, and numerous moist râles were heard over this area anteriorly. One specimen of sputum was negative for tubercle bacilli. *Diagnosis:* Pulmonary tuberculosis, moderately advanced. *Recommendation:* Sanatorium treatment.

This patient was sent to a sanatorium for five months, was discharged for two weeks, during which time a pleural effusion was discovered, and was returned to the sanatorium, where she still remains.

K2: Girl, American, aged 15 years. Weight, 81 per cent. Tuberculin test not made. *X-ray examination:* On the right there was dense infiltration in the upper third and moderately dense infiltration throughout the rest of the lung. On the left there was dense infiltration in the upper third and scattered infiltration in the middle third. The heart was displaced to the right. On physical examination there was diminished expansion and diminished resonance over both lungs. Breath-sounds were bronchovesicular at both apices, with increased transmission of voice sounds over the upper third of the right lung. Numerous moist râles were heard throughout both lungs. Two years before this examination, this girl was said to have had pneumonia, remaining at home for six months, and subsequently she has had cough with expectoration. She had constant fatigue and dyspnoea on slight exertion. Temperature, 101.6° at 12 M. *Diagnosis:* Pulmonary tuberculosis, far advanced. *Recommendation:* Sanatorium treatment.

This girl was taken from school. During the month after her examination three specimens of sputum were positive for tubercle bacilli. She died about four months after the examination.

K3: Girl, Jewish, aged 15 years. Weight, 95 per cent. Tuberculin reaction, ++ to 0.01 mgm. *X-ray examination:* There was moderately dense soft infiltration in the right apex extending as low as the 4th rib. In the 4th interspace there was a cavity about 2 cm. in diameter. Physical examination showed diminished resonance over the upper third of the right lung anteriorly with increased vocal resonance and whispered voice. Breath-sounds were bronchovesicular. Posteriorly at the right apex there was a slight increase of vocal resonance and whispered voice accompanied by definite fine moist râles. Temperature, 98.4° at 10 A.M. *Diagnosis:* Pulmonary tuberculosis, moderately advanced. *Recommendation:* Sanatorium treatment.

At an examination four months later the infiltration was found to have increased in density and the cavity had increased in size. No sputum could be obtained. This girl refused to leave school and with altered regimen improved over a further period of four months. She gained in weight, the density of the infiltration lessened, and the cavity contracted.

K4: Girl, Italian, aged 18 years. Weight, 95 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* On the right side there was scanty infiltration at the apex in the 2nd

interspace and moderately dense soft infiltration between the 3rd and 5th ribs toward the axilla. In the left lung there was a nodule in the 7th interspace and two moderately large calcified masses in the hilum. On physical examination there was diminished resonance at the apex of the right lung both anteriorly and posteriorly, with fine moist râles. *Diagnosis:* Pulmonary tuberculosis, minimal, and tuberculosis of the lymph nodes with calcified nodule. *Recommendation:* Sanatorium treatment.

This girl refused sanatorium care and continued with her education after graduating from high-school. She has had X-ray films over a period of 17 months, and the lesion has shown steady progression although it has not yet produced ill-health.

K5: Girl, Jewish, aged 15 years. Weight, 89 per cent. Tuberculin reaction, + to 0.01mgm. *X-ray examination:* There was moderately dense soft infiltration at the left apex in the second and third interspaces. Physical examination revealed slightly diminished resonance at the left apex and diminished expansion over the whole left side. Temperature, 98° at 9.30 A.M. *Diagnosis:* Pulmonary tuberculosis, minimal. *Recommendation:* Sanatorium treatment or supervision.

This girl continued with her school work under a modified regimen and spent three summer months in a preventorium. X-ray films one year after the first examination showed no spread of the lesion, and 17 months after examination the girl appears to be still perfectly well.

K6: Girl, Jewish, aged 16 years. Weight, 95 per cent. Tuberculin reaction, ++ to 0.01 mgm. *X-ray examination:* There was moderately dense infiltration at the right apex extending as low as the 5th interspace. There was also a nodule at the base and a calcified area in the hilum. There was infiltration at the left apex as low as the 5th interspace, denser in the medial half. There was also a nodule at the base with a calcified area in the hilum. Physical examination revealed diminished expansion at the right apex and diminished resonance at both apices, more marked on the right side. Temperature, 96.5° at 11 A.M. *Diagnosis:* Pulmonary tuberculosis, minimal, and tuberculosis of lymph nodes with peripheral calcified nodule. *Recommendation:* Sanatorium treatment.

K7: Girl, Italian, aged 16 years. Weight, 105 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was moderately dense soft infiltration at the left apex extending as low as the 5th rib. Physical examination showed lessened movement in the upper half of the chest on the left side anteriorly and diminished resonance at the left apex posteriorly. Temperature, 97.3° at 12.15 P.M. This girl had a sister-in-law with pulmonary tuberculosis. *Diagnosis:* Pulmonary tuberculosis, minimal. *Recommendation:* Sanatorium treatment.

She was reëxamined one year later. There had been an increase in the area and in the density of the infiltration. She continued with school but rested whenever possible at home. The lesion during the past four months has retrogressed somewhat but is still considered a serious danger to the health of the patient.

K8: Girl, Italian, aged 17 years. Weight, 87 per cent. Tuberculin reaction, ++ to 0.01 mgm. *X-ray examination:* There was thickening of the pleura at the right apex with scattered soft infiltration in the 3rd and 4th interspaces. Physical examination revealed diminished expansion and loss of resonance at the right apex. Temperature, 97.4° at 11.30 A.M. An uncle was in close contact with this girl until she was six years old, when he died of tuberculosis. She also had been in occasional contact with a cousin who died of tuberculosis four years ago. She had had an X-ray examination two and one-half years ago, which showed no abnormality. *Diagnosis:* Pulmonary tuberculosis, minimal. *Recommendation:* Sanatorium treatment.

SCHOOL K (HIGH SCHOOL FOR GIRLS)

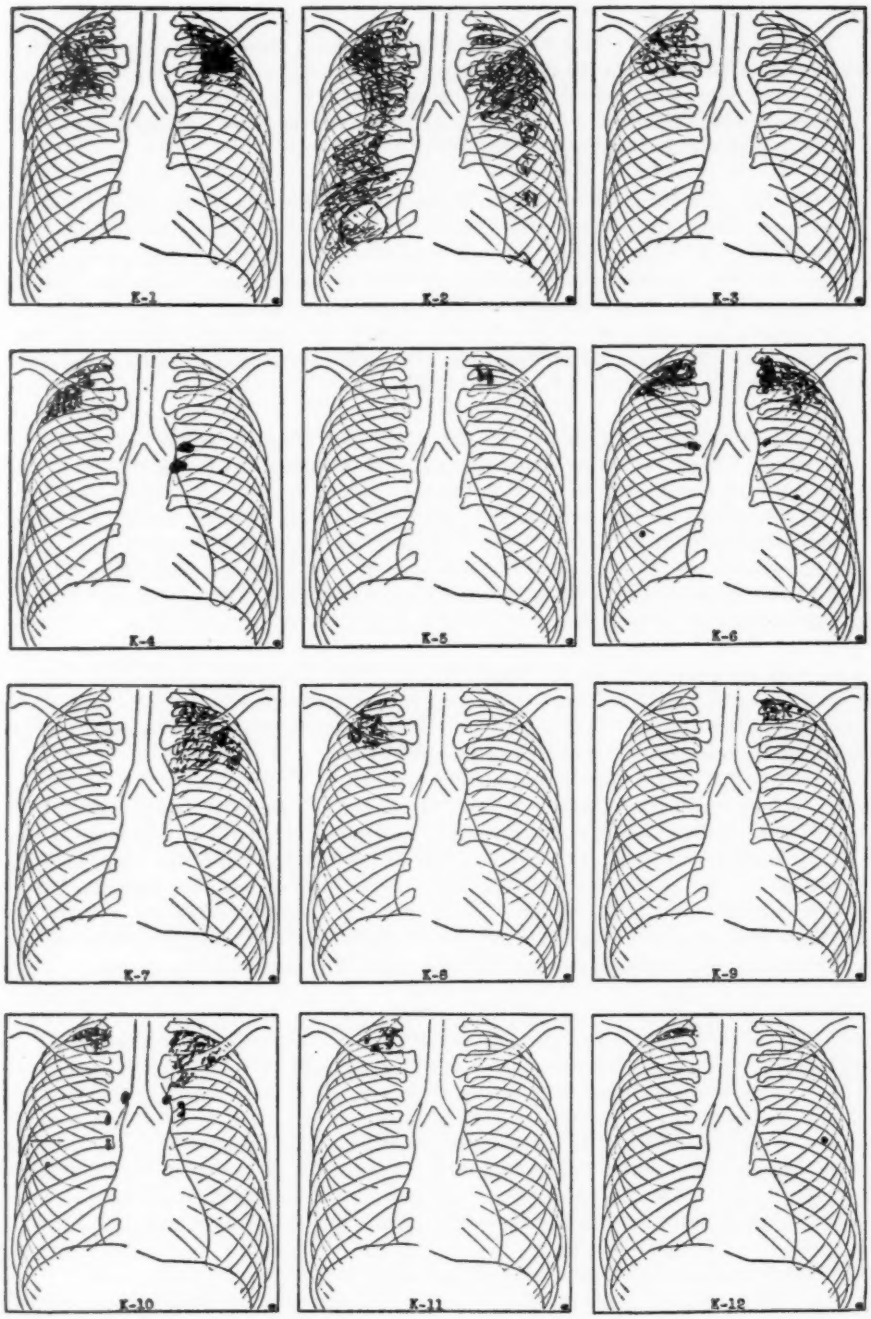

PLATE I

This girl continued in school for six months. Her lesion showed no progression. She was sent to a preventorium for seven months, where she was ambulant most of the day. On discharge from the preventorium her lesion was found to be more extensive and flocculent in appearance in the X-ray film. Rest in bed at home was instituted. X-ray examination two months later showed no definite change.

K9: Girl, Italian, aged 18 years. Weight, 96 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was scattered soft infiltration in the left apex extending as low as the 4th rib. The infiltration was denser in the medial half of the apex. Physical examination revealed less expansion and diminished resonance at the left apex. *Diagnosis:* Pulmonary tuberculosis, minimal. *Recommendation:* Sanatorium treatment.

This girl would not go to a sanatorium but agreed to remain under supervision. She increased her hours of rest. X-ray films taken 19 months later showed the lesion in the same area as before but strand-like and apparently inactive.

K10: Girl, American, aged 15 years. Weight, 91 per cent. Tuberculin reaction, +++ to 0.01 mgm. *X-ray examination:* There was scattered infiltration at the right apex in the second and third interspaces, more marked in the mesial half. There was also a nodule at the 8th rib and several calcified masses at the hilum. On the left side scanty infiltration at the apex extended as low as the 5th rib. There was a nodule in the 6th and another in the 8th interspace. No physical signs. Temperature, 97.6° at 10.45 A.M. *Diagnosis:* Latent apical tuberculosis, extending below the clavicle, with peripheral calcified nodules. *Recommendation:* Sanatorium treatment.

K11: Girl, Italian, aged 15 years. Weight, 93 per cent. Tuberculin reaction, ++ to 0.01 mgm. *X-ray examination:* There was scattered soft infiltration in the first and second interspace at the right apex. No physical signs. Temperature not taken. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle.

K12: Girl, Italian, aged 15 years. Weight, 94 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was a nodule at the level of the 4th rib anteriorly on the left, and scanty infiltration at the right apex in the 2nd interspace. No physical signs. Temperature, 98.2° at 10 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle, and peripheral calcified nodule. *Recommendation:* Supervision.

X-ray films 19 months later still show apical infiltration. There is no definite change and the appearance of the lesion suggests that it may still be potentially dangerous.

PLATE II

School K (High-School for Girls) (Concluded)

K13: Girl, Jewish, aged 16 years. Weight, 92 per cent. Tuberculin reaction, +++ to 0.1 mgm. *X-ray examination:* There was thickening of the pleura at the left apex with scanty areas of infiltration in the 2nd and 4th interspaces. No physical signs. Temperature, 97.8° at 10.30 A.M. *Diagnosis:* Latent apical tuberculosis, extending below the clavicle. *Recommendation:* Supervision.

K14: Girl, Jewish, aged 16 years. Weight, 111 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was a nodule at the base of the right lung. There was thickening of the pleura at the left apex with scanty infiltration in the 2nd interspace. There was also a nodule in the 4th interspace with a calcified mass at the hilum. No physical signs. Temperature, 98.6° at 11 A.M. When this girl was four years old her mother died of tuberculosis. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle, with tuberculosis of the lymph nodes and peripheral calcified nodule. *Recommendation:* Supervision.

K15: Girl, Jewish, aged 16 years. Weight, 78 per cent. Tuberculin reaction, + to 0.1 mgm. *X-ray examination:* There was thickening of the pleura at the right apex with salients projecting into the lung. There was scattered infiltration in the 2nd and 3rd interspaces on the left side. No physical signs. Temperature, 98.8° at 11 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision.

K16: Girl, Italian, aged 16 years. Weight, 103 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was moderately dense soft infiltration at the right apex in the 2nd interspace and strand-like infiltration as low as the 5th rib. There was a small area of strand-like infiltration at the left apex. No physical signs. Temperature, 98.2°. *Diagnosis:* Latent apical tuberculosis, extending below the clavicle. *Recommendation:* Supervision.

K17: Girl, Italian, aged 16 years. Weight, 97 per cent. Tuberculin reaction, + to 1.0 mgm. *X-ray examination:* There was a small area of scanty infiltration at the left apex in the 2nd interspace. No physical signs. Temperature, 97.4° at 12 M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision.

K18: Girl, Italian, aged 16 years. Weight, 111 per cent. Tuberculin reaction, + to 0.1 mgm. *X-ray examination:* There was thickening of the pleura at both apices with salients extending into the lung tissue. No physical signs. Temperature, 98.8° at 9.30 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision. X-ray examination 14 months later showed the lesion unchanged.

K19: Girl, Jewish, aged 17 years. Weight, 89 per cent. Tuberculin reaction, ++ to 0.01 mgm. *X-ray examination:* There was moderately dense infiltration at the left apex extending as low as the 4th rib. No physical signs. Temperature, 97.5°. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Sanatorium treatment.

This girl did not go to a sanatorium, but has been under constant medical supervision with modified regimen for 19 months. There has been no definite change in the lesion, the appearance in the film suggesting that it remains a serious menace to health.

K20: Girl, colored, aged 17 years. Weight, 95 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was a small wedge-shaped area of infiltration extending into the lung tissue in the 2nd interspace at the right apex. No physical signs. Temperature, 98° at 10.15 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision.

K21: Girl, Jewish, aged 17 years. Weight, 92 per cent. Tuberculin reaction, + to 1.0 mgm. *X-ray examination:* There was thickening of the pleura at the left apex with scanty infiltration as low as the 4th rib. No physical signs. Temperature, 96° at 11.30 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision.

K22: Girl, Irish, aged 17 years. Weight, 98 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was scattered infiltration at the right apex in the 2nd and 3rd interspaces. No physical signs. Temperature, 98.4°. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision.

K23: Girl, Jewish, aged 17 years. Weight, 103 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was a small area of dense infiltration with calcium deposition at the right apex in the second interspace. No physical signs. Temperature, 98.2° at 10 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision.

K24: Girl, Jewish, aged 17 years. Weight, 102 per cent. Tuberculin reaction, + to 0.01 mgm. *X-ray examination:* There was scattered strand-like infiltration at the right apex extending as low as the 4th rib and two calcified areas at the hilum. There were also several calcified spots in the soft tissue of the neck on the left side. No physical signs. Temperature, 97.6° at 10 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle, and multiple tuberculosis of the lymph nodes with a peripheral calcified nodule. *Recommendation:* Supervision.

K25: Girl, Jewish, aged 17 years. Weight, 90 per cent. Tuberculin reaction, ++ to 0.01 mgm. *X-ray examination:* There was soft infiltration at the right apex in the 2nd interspace. No physical signs. Temperature, 98° at 11 A.M. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Supervision.

K26: Girl, Jewish, aged 17 years. Weight, 88 per cent. Tuberculin reaction, + to 1.0 mgm. *X-ray examination:* There was thickening of the pleura at the left apex with salients projecting into the lung in the second interspace. No physical signs. *Diagnosis:* Latent apical tuberculosis, not extending below the clavicle. *Recommendation:* Observation.

SCHOOL K (HIGH SCHOOL FOR GIRLS) CONTINUED

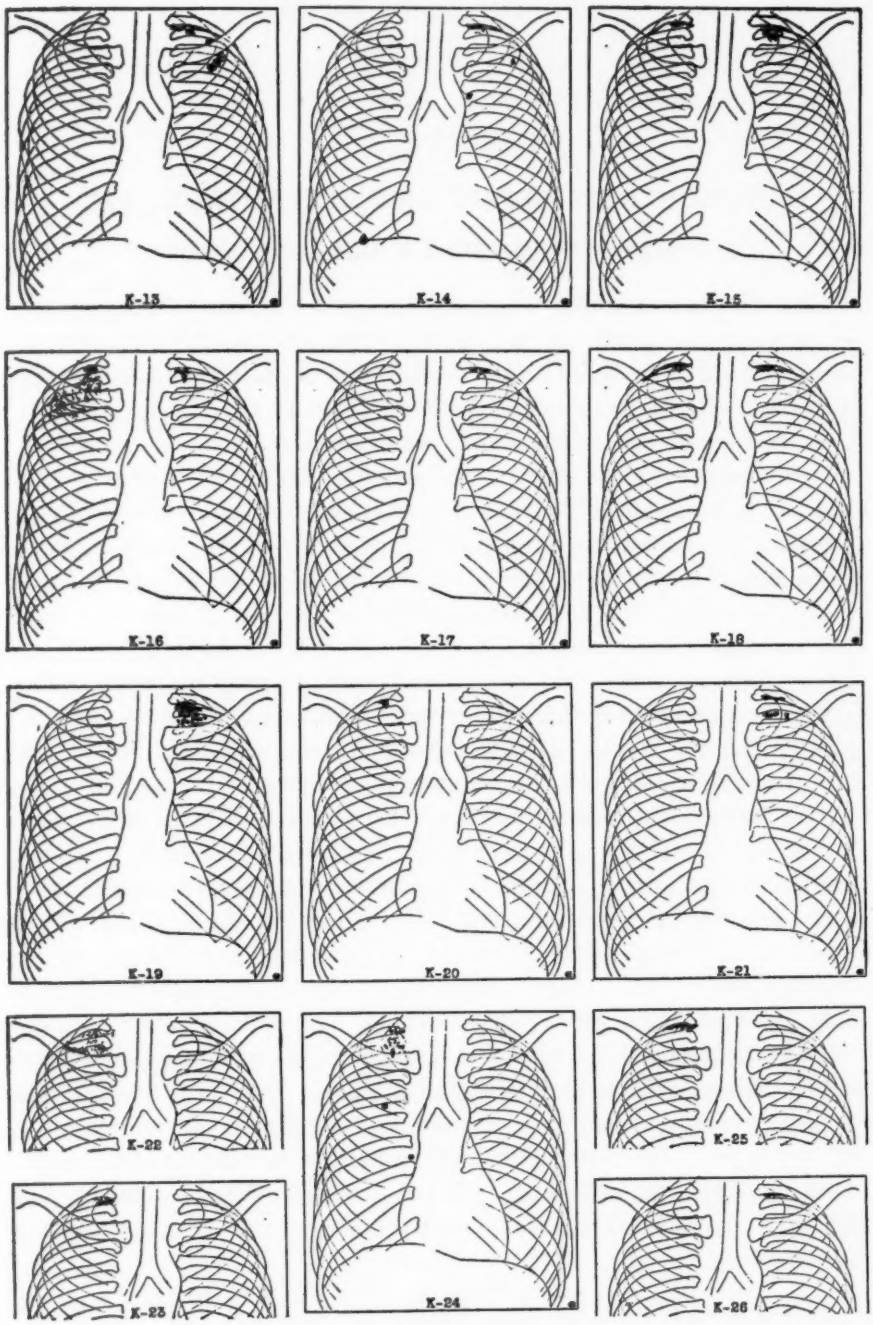

PLATE II

TUBERCULOSIS CLINIC AND CONTACT STUDY[1]

DOROTHY E. WIESNER[2] AND S. MARGARET SMITH[3]

When Sir Robert Philip founded the Royal Victoria Dispensary for Consumption in Edinburgh in 1887, five years after Koch's discovery of the tubercle bacillus, he included the visitation of patients in their homes for the purpose of treatment and investigation of the risk of infection as one of the objects of his tuberculosis dispensary.

Ever since that time chest clinics have continued to emphasize the necessity of having household contacts of tuberculous patients examined. The purpose of contact examinations is primarily to find early cases of tuberculosis and put them under care, so that they may recover and not in turn infect others. The amount of time and effort spent on this aspect of tuberculosis work is costly in both money and energy.

It is believed that all the time and effort devoted to securing the examination of contacts have been well spent. It is almost taken for granted that the results of this work have been excellent. But at the time of the Hospital and Health Survey it appeared that in Philadelphia only 30 per cent of the household contacts of patients diagnosed tuberculous at our chest clinics as a whole were actually examined. Figures from other localities in which studies were made show remarkable variations—one district described as "just an average county so far as tuberculosis is concerned" had examined 20 per cent, and Fargo, North Dakota (which was a demonstration city under the Commonwealth Fund), had examined 60 per cent.

These variations suggested that a further intensive analysis of the contact work of a single clinic would be of value. How large a percentage of contact examinations was secured in this clinic? Were adults or children more likely to respond to the invitation and urging of the clinic workers,—white or colored,—male or female? What influence did the stage of sickness of the first patient play in securing contact examinations?

[1] Read at the Philadelphia Tuberculosis Conference, November 15, 1932.

[2] Philadelphia Health Council and Tuberculosis Committee.

[3] Henry Phipps Institute, Philadelphia, Pennsylvania.

Answers to these questions would throw light upon this objective of clinic work. Further help would be secured by such a study in the information gained as to why so many contacts do not come to clinic. Data would also be afforded as to how much tuberculosis was found among those who were examined.

The clinic whose records were studied as a basis for this report was that of the Henry Phipps Institute which offered them for this investigation hoping that the study would stimulate its workers to analyze further the difficulties of contact work and that it would be of use to other tuberculosis clinics in the city.

The method followed was to make out a card for each patient diagnosed tuberculous for the first time at the Henry Phipps Institute in the 18 months between January 1, 1930, and June 30, 1931. These patients were called "the original tuberculous patients," although in some households there were other patients previously diagnosed as tuberculous. Upon the card were entered the data concerning the patient himself and the names of all household contacts. A household contact was any person living in the dwelling and eating at the same table at the date of diagnosis of the original patient.

At the first anniversary of the date of diagnosis of "the original tuberculous patient," the family record was reviewed, and the dates of examination of such contacts as had been examined with the results of the examinations were entered on the card. Information was also secured at this time from the field-nurse visiting the family as to the reasons why the others had not come to clinic. Thus each record represents a twelve months' attempt on the part of the family and clinic to secure the examination of contacts.

There were 182 "original tuberculous patients" in the Phipps clinic district who were diagnosed tuberculous for the first time in the 18 months being studied, for whom follow-up was attempted. About two-thirds of these were white and one-third colored. The white group were largely either foreign-born or native-born of foreign parentage. Only 11 were of native-born parentage. Fifty were Italians, 34 were Hebrews of families from Russia, Roumania, and Austria. There were 5 patients each from Polish and German families. Three were of Irish parentage, 3 Swedish, and one each was from England, Spain, and Greece. Many of the Negro group were of the transient type—adult individuals living in households to which they had no tied relationship. Families of 33 of the white patients and of 27 of the colored were known to one or more of the relief agencies of the city.

Four-fifths of the 182 original tuberculous patients were young adults, that is, 16 to 49 years of age; about three-fifths were males and two-fifths females. Of these patients 23 per cent were diagnosed as having minimal tuberculosis, 38 per cent moderately advanced, and 39 per cent far-advanced tuberculosis.

There were 647 household contacts of the 182 original tuberculous patients; that is, between three and four per patient. For 27 of the 182 patients there were no household contacts, and for 22 only one. Of the white patients there were 22 having three household contacts, 22 being

TABLE 1

Original tuberculous patients by color, age and sex according to stage of tuberculosis and by sputum reports

PATIENTS BY COLOR, AGE AND SEX	TOTAL PATIENTS	PATIENTS BY STAGE OF TUBERCULOSIS				PATIENTS BY SPUTUM REPORTS			
		Minimal	Moderately advanced	Far advanced	Other	Sputum positive	Sputum negative	No sputum	All others
Total patients	182	42	68	71	1	79	54	35	14
White	114	31	50	33	—	44	32	26	12
Colored	68	11	18	38	1	35	22	9	2
Under 16 years	10	4	4	2	—	3	1	6	—
16–49	147	35	51	60	1	67	42	25	13
50 and over	25	3	13	9	—	9	11	4	1
Male	102	22	38	41	1	47	31	13	11
Female	80	20	30	30	—	32	23	22	3

the largest number in any one group of this sort. There were 19 having four household contacts, 14 having five household contacts, and so forth. Among the colored, however, families seem to be smaller. This is perhaps surprising, but it is indicative of the type of colored population living in the Phipps clinic district. The largest number of colored patients falls in the group having one contact only. There were 15 patients who had one contact, 12 who had two, 6 who had three, and so forth. The distribution of contacts shows that the 114 white patients had 446 household contacts, an average of 3.9; and the 68 colored patients had 201, an average of 3.0. Furthermore, of the 446 contacts of white patients the percentage of adults was 56 and of colored 58. Thus the

usual factor of more children in the colored families does not hold in the Phipps district. It is therefore not possible to generalize too freely from these statistics of the contacts of patients diagnosed at the Henry Phipps Institute because it is evident that the families, particularly the Negro families, are not what one would find in the 47th Ward or in West Philadelphia. The size of the family shows this as well as the high percentage of adult contacts.

PART I. HOUSEHOLD CONTACTS EXAMINED

What were the results of the efforts in the clinic to secure contact examinations? In each case 12 months passed before the record was completed. The tabulation of the contacts thus examined shows that 308, or 48 per cent, within the year after the date of diagnosis of the "original tuberculous patient," had come to the clinic. This 48 per cent is higher than the figure of 30 per cent for the city as a whole, which was found at the time of the Hospital and Health Survey, and much higher than the 20 per cent in the district described as "just an average county," but not so high as the 60 per cent in the demonstration city.

Of the contacts of white patients, 45 per cent were examined. Of the contacts of Negro patients, 53 per cent were examined. The Negroes thus seem to respond more readily. Reasons for this may be that a far greater percentage of the original patients were in the advanced and far-advanced stages of the disease, 56 per cent of the colored patients being diagnosed far advanced and only 29 per cent of the whites.

When the results of contact examinations are considered according to the ages of the contacts, the well-known fact that it is easier to get children than adults to clinics shows itself again. Sixty-four per cent of children were examined in the 12 months after the diagnosis of the first patient, but only 35 per cent of the adults.

When the contacts to be examined are separated into male and female, it is seen that 50 per cent of the males were examined and only 45 per cent of the females. This does not bear out the opinion that it is easier to get women to clinic than men, although the difference is not so marked as the difference between adults and children.

When these examination figures are studied by the size of the household there is some evidence that the larger the family the more likely is one able to secure examinations of contacts. In families in which there were more than five contacts to be examined 50 per cent or more of the contacts were brought to clinic. In families in which there were

six contacts 56 per cent were examined; in families in which there were seven contacts 50 per cent were examined; in families in which there were 8 contacts 55 per cent were examined; and in families in which there were 9 contacts 56 per cent were examined. In the smaller families the contacts to be examined were usually adults and in the larger families the contacts were more often children. This is one explanation for the greater number of examinations in large families.

An analysis of time between diagnosis of the original patient and examination of the contact shows that 28 per cent of the contacts were

TABLE 2

Contacts of original tuberculous patients by color, age and sex of the contacts, according to the time between diagnosis of patient and examination of contact

CONTACTS TO BE EXAMINED BY COLOR, AGE AND SEX	TOTAL CONTACTS TO BE EXAMINED	EXAMINATION OF CONTACTS BY TIME BETWEEN DIAGNOSIS AND EXAMINATION									
		Less than one month				1 month (31–59 days)	2 months (60–89 days)	3–5 months (90–179 days)	6–8 months (180–269 days)	9–12 months (270–365 days)	Not examined within year
		Total within 1 month	1–6 days	7–13 days	14–30 days						
Total contacts	647	183	65	74	44	28	22	36	21	18	339
White	453	118	46	53	19	19	16	21	15	13	251
Colored	194	65	19	21	25	9	6	15	6	5	88
Under 16 years	282	116	43	51	22	17	11	19	10	7	102
16 and over	365	67	22	23	22	11	11	17	11	11	237
Male	319	92	34	38	20	18	10	18	12	10	159
Female	328	91	31	36	24	10	12	18	9	8	180

examined within 30 days of the date of diagnosis of the first patient, and that this figure increased very slowly after the first 30 days. In the first and second months after diagnosis of the first patient 33 per cent were examined, by the end of the third month 36 per cent were examined, by the end of the sixth month 42 per cent were examined, by the end of the ninth month 45 per cent, and by the end of the year the total of 48 per cent. Thus it is evident that the first month is the most fruitful time for contact-examination work when the family has become aware of the sickness of the patient and is learning about tuberculosis. There is a slight tendency for the colored to delay coming into the clinic in the

first weeks after the diagnosis of the original patient, although by the end of the first month 34 per cent of the colored contacts were examined and only 26 per cent of the whites. The children immediately made a better showing, 15 per cent of the children being examined within the first week and only 6 per cent of the adults. By the end of the first month 41 per cent of the children were examined and 18 per cent of the adults.

The seriousness of the lesion of the original patient as well as the sputum reports influence both the family's attitude toward the need of examination and the physician's and nurse's endeavors to get the contact to clinic. There were 168 contacts of patients with minimal

TABLE 3

Examination of contacts of original tuberculous patients, by stage of tuberculosis of original patients and by diagnoses of examined contacts

ORIGINAL PATIENTS BY STAGE OF TUBERCULOSIS	TOTAL PATIENTS AND TOTAL CONTACTS				CONTACTS BY RESULTS OF EXAMINATIONS									
	Original patients	Contacts			Diagnosed tuberculous		Latent tuberculosis		Diagnosis undetermined		Diagnosed non-tuberculous		Not examined	
		Total	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children
Total original patients	182	647	365	282	10	9	11	5	4	3	103	163	237	102
Minimal tuberculosis	42	168	83	85	5	1	2	—	—	—	12	33	64	51
Moderately advanced	68	257	155	102	4	3	6	1	2	1	54	76	89	21
Far advanced	71	217	126	91	1	5	3	4	2	2	36	50	84	30
Others	1	5	1	4	—	—	—	—	—	—	1	4	—	—

tuberculosis, of whom 32 per cent were examined. There were 257 contacts of patients with moderately advanced tuberculosis, of whom 57 per cent were examined. There were 217 contacts of patients with far-advanced tuberculosis, of whom 48 per cent were examined. This shows that there is less likelihood of getting the contacts of patients with minimal tuberculosis examined. Why the percentage of examination of contacts of patients with moderately advanced tuberculosis was higher than the examination of contacts of the patients with far-advanced tuberculosis is not easily explicable. In some instances the far-advanced patient was removed from the household soon after diagnosis, either to an institution or by death, and in such families the contacts often

minimize the dangers of tuberculosis and do not readily submit to examination.

So far as the sputum reports of the first patient are concerned, there were 43 per cent of the original 182 patients who had positive sputum, 30 per cent who had negative sputum, 8 per cent whose sputum had not been tested often enough to warrant a classification, and 19 per cent who had had no sputum examination. The patients with positive sputum had 282 contacts, of whom 59 per cent were examined. The patients with negative sputum had 199 contacts, of whom 44 per cent were examined. The patients whose sputum had not been examined had 119 contacts, of whom only 29 per cent were examined.

Summary

This analysis of household contacts examined shows that the most complete contact-examination work will be possible in districts serving large families with many children, colored families, and families with advanced tuberculosis patients with positive sputum. These are the factors that can be measured to some extent at least. Every clinic worker knows that, in addition to these, the more intangible factors of atmosphere of the clinic as well as personalities of the physicians and nurses play an extremely important part.

PART II. REASONS FOR NO EXAMINATIONS

Turning now from the study of contacts examined to a consideration of the reasons for no examinations we find interesting data. Statistics on contact examinations, so far as they have come to our notice from any source, have been very critical of the number of contacts examined. It is held that all of the contacts should be examined. The 48 per cent of contacts examined in this study would be held to be low by these standards. But studies of the reasons why household contacts did not come for examinations have not been made, so far as we know, to determine what the actual situation is. A study of these reasons shows need for the modification of the standard of 100 per cent of contact examinations and throws new light on the difficulties of this work.

In an effort to learn why the contacts did not come to the clinic at least one explanation about each person who did not come during the twelve months after the diagnosis of the original tuberculous patient was insisted upon. In many cases there were various explanations for this, and the one was chosen which the nurse considered most difficult to

overcome. In some cases the nurse had difficulty in stating reasons, but finally did so. Forcing these explanations into such form that they could be used in a statistical manner may not be entirely justified, but more was learned about these difficulties than if the questioning had been less insistent.

Of the 647 contacts to be examined there were 339 who did not come to clinic during the 12 months following the diagnosis of the original patient.

There are three reasons which account for 60 per cent of these omissions. The first of these is that the contact either was examined by a private physician or physician in some other clinic, or promised the tuberculosis-clinic staff that he would be. There were 51 who wished the services of the private physicians and 20 who wished to continue with the physician in some other clinic. These 71 account for one-fifth of the total number of those who did not come to clinic within 12 months.

The second reason in numerical size is one that is extremely baffling. There were 68 contacts who promised the tuberculosis clinic that they would come to clinic (for the most part accepting appointments in clinic time) but who had not kept their promises up to the end of the twelfth month. The doctor and nurse could only continue their efforts with such families, although the figures by length of time between diagnosis of original patient and examination of contact show that after the first 30 days there is far less likelihood of securing contact examinations. This group of 68 also comprises about one-fifth of the total who were not examined.

The third reason is one of particular interest to organizations interested in health education. There were 64 persons who reiterated that they could see no need for an examination because they felt well. This group, and the preceding one, show definitely that there are many who are not easily impressed about the need of early examination. It will be the task of all to devise new methods of assisting the tuberculosis worker in impressing the need of early examination on those who have been in contact with the disease regardless of symptoms. Often the records show that, when the contact did feel the need of examination, active disease was present. These persons who were not examined because they felt well and saw no need of examination also comprise about one-fifth of the total contacts who were not examined.

There were fourteen other kinds of reasons given for no examination, but none of them approached these three in numerical importance.

These reasons include a group of 23 contacts who were never located; 22 who absolutely refused examination and refused to give a reason also; 17 who feared either the clinic treatment or the humiliation of being a clinic patient, or to have the neighbors learn that there was tuberculosis in the family, or to know they themselves had tuberculosis; 13 young children who were not taken by the parent; 13 who left the household before the nurse could persuade them to come to clinic; 12 contacts who could not leave their homes because of physical or mental conditions; and 11 who were examined either one month before or after the twelve months included in this study.

The remainder of these reasons making up about 8 per cent of the total include contacts who though living in the household were never seen by the doctor or nurse; one household in which the original patient remained only a few days; a few contacts who would not leave work to come to clinic; mothers who could not leave small children; and there were some contacts who died.

A review of the list of reasons for no examination shows that a number of them are of a character beyond the control of clinic personnel. Some contacts moved from the household almost as soon as the original patient was diagnosed tuberculous. Some were unable to leave the house because of physical or mental conditions. Some were never at home when the nurse visited. In some cases the source of infection had been in the household but a few days and was immediately removed. Some contacts were working and since there was no night clinic during part of this time they could not be examined. Unfortunately some died. All of these reasons are beyond the control of the nurse, but this study would indicate that not over 13 per cent fall in the class of contacts who could not possibly be examined in the clinic.

The three leading reasons vary considerably according to color. Among the white contacts there were 27 per cent who preferred to be examined by a private physician or physician in some clinic they were already attending. Among Negroes only 5 per cent gave as the reason for not coming to clinic that they preferred examination by other physicians. However, there were 34 per cent of the Negroes who promised to come to clinic, but who did not keep their promises, as compared with only 15 per cent among the whites.

The reasons vary less strikingly when the factor of age is considered. There was a greater proportion of children who came in the first group "examined by other physician or promised to be," and also a greater proportion who did not keep their appointments at the Phipps Clinic.

So far as sex is concerned, the women were more apt to prefer their private physician, and the men to give the reason that they felt well and therefore saw no need of examination.

The contacts of the original patients diagnosed minimal tuberculosis were more apt to feel that there was no need of examination for them. These households are extremely difficult to persuade that there is real danger, because the original patient himself is often not sufficiently sick to evince the hazard of infection. The factor of sputum shows that in households where the original patient had positive sputum there was more recognition of the need of examination. It is rather surprising, however, to see that there were 20 contacts in households with positive-sputum patients who did not come to clinic because they felt well and saw no need for examination.

Summary

The three obstacles most frequently met in endeavors to secure contact examination are (1) that the contact wishes to be examined by a private physician or a physician in some clinic he is already attending; (2) that the contact will promise to come to clinic and accept a clinic appointment, but not actually present himself; and (3) that the contact says he feels well and sees no need for examination. Recognition of the importance of these three reasons, which account for 60 per cent of the failures to secure examinations, is the first step towards overcoming them. By discussions of ways in which the difficulties may be met, it will perhaps be possible to lower the percentage of no examination and thus save further sickness and infection in tuberculous families. It must be recognized, however, that about 13 per cent of the contacts could not be examined in the clinic for reasons beyond the control of the nurse or physician.

PART III. TUBERCULOSIS FOUND IN CONTACT-EXAMINATION WORK

Notwithstanding these difficulties this study shows that contact examination is a most important field of tuberculosis work when the amount of tuberculosis found among contacts is considered.

Of the contacts examined within 12 months of the diagnosis of the first patient, 11.4 per cent were found to be tuberculous, and the diagnoses of 2.3 per cent were undetermined at the end of the 12-month period. That is, there was one tuberculous patient in every nine contacts examined.

In X-ray examinations in schools about 1 per cent of the girls and boys examined are found to be tuberculous. The group of contact cases in the clinic, however, is a group which is known to have been exposed to infection. Since over 11 per cent of such persons are found to have tuberculous lesions, efforts to examine all contacts is one of the most valuable methods of case-finding.

There was a greater proportion of tuberculosis found among contacts in colored families than among whites,—13 per cent among the colored, and 10 per cent among the whites. Among the children only 8 per cent were found tuberculous, but among adults 16 per cent. Eleven per cent of the males were found to be tuberculous and 12 per cent of the females.

The findings of the analysis by stage of tuberculosis of the original patient is at first confusing, a greater percentage of tuberculosis being found among the contacts of the original patients with minimal tuberculosis than among the contacts of patients with moderately advanced and far-advanced tuberculosis. This is due to the fact that the "original tuberculous patients" were not always the first patients ever diagnosed in the family. This means that often the so called "contact" may be the true source of infection, and the person diagnosed as the original tuberculous patient may have contracted it from him. In other words, our terms of "original tuberculous patient" and "contact" are only convenient terms limited by the time-element in order that we may have a place to start a family study. This point of view is the necessary one for clinic workers to hold in their contact work.

Among the contacts of positive-sputum patients 12.0 per cent were found to be tuberculous, and among the contacts of negative-sputum patients 10.3 per cent. But among the contacts of patients whose sputum was not examined 14.3 per cent were found to be tuberculous. This is probably for the reason just mentioned.

There were 35 contacts found to be tuberculous. The diagnoses of these 35 persons a year after the date of diagnosis of "the original tuberculous patient" were as follows: 17 had latent tuberculosis, that is, tuberculosis demonstrable by X-ray examination only; 8 had minimal tuberculosis, 7 had moderately advanced tuberculosis, 2 had far-advanced tuberculosis, and 1 had miliary tuberculosis.

About two years after the first of the original patients were diagnosed, a review of the status of the total 647 contacts was made. It was found that 28 additional contacts had been examined, of whom 8 were found to be tuberculous, 4 having diagnoses of latent tuberculosis, 2 of moder-

ately advanced tuberculosis, and 2 of far-advanced tuberculosis. There were also 5 contacts who had been negative in the 12-month period, but whose conditions were later found to be tuberculous, four of these now being diagnosed as having moderately advanced tuberculosis, and one far advanced. There were changes also among those diagnosed in the first twelve months' period.

Summary

The status of the entire group of 647 contacts at this time was as follows: Examined, 336, or 51.9 per cent, and, of these, 50, or 14.8 per cent, were tuberculous. Of these 50 persons, 18 were still diagnosed as having latent tuberculosis; 8 as having minimal tuberculosis; 13 as having moderately advanced tuberculosis; 4 as having far-advanced tuberculosis; and 7 had died of tuberculosis.

CONCLUSION

This study of the contacts examined, the reasons for others not being examined, and the results of such examinations reflects to some extent similar conditions in other clinics of the city and opens for discussion one of the vital problems of tuberculosis control in Philadelphia, a problem which deserves increased consideration from all tuberculosis workers.

A TUBERCULOSIS SURVEY AMONG 2,000 FOOD-HANDLERS IN NEW YORK CITY

D. CLIFFORD MARTIN,[1] HARRY T. PESSAR[2] AND JACOB A. GOLDBERG[3]

INTRODUCTION

In New York City the practice of a systematic physical examination of food-handlers was put into operation by the Department of Health, Division of Industrial Hygiene, in August, 1915, in conformity with a new provision of the Sanitary Code, requiring that food-handlers obtain a certificate showing that they were free from infectious diseases in a communicable form. Examinations at first were limited to food-handlers in hotels, restaurants, and other food-preparing establishments. Subsequently this regulation was extended to include all those who handled food in hospitals, foundling asylums, and similar institutions, in order to protect invalids and children from persons suffering from communicable diseases. This system of examining food-handlers was later adopted by most large cities of the country.

The first attempt to analyze the findings among food-handlers was incorporated in a study published in 1917, entitled *The Health of Food-Handlers*. This report was drawn up by Dr. Louis I. Harris, at that time Director of the Bureau of Preventable Diseases in the Department of Health, and Dr. Louis I. Dublin, Statistician in the Metropolitan Life Insurance Company. A special study was instituted of careful examinations of 1,980 cases, of which a fairly intensive physical examination was made. As noted in the report, these cases were in no sense selected, except for the completeness of both the examination and the record.

A large number of physical defects was found and reported upon. The number of cases of tuberculosis found in this study was reported as being very low. Ten cases with active pulmonary tuberculosis were diagnosed among 1,980 food-handlers examined, with the rate of 0.51 per cent for all the workers. Of this number, 7 were males and 3 were

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females. In addition, the authors reported 3 cases of arrested tuberculosis among the males, making a total of 13 cases, or 0.66 per cent for all the workers. If all active, arrested and suspected cases were grouped together, the total number of cases of pulmonary tuberculosis was given as 25, or a prevalence-rate of 1.26 per cent for all the workers.

It is important to indicate that in this particular study note was made of the results of the somewhat careful physical examinations made upon the 1,980 cases as compared to what is termed in the report "unavoidably hurried routine examination given the 32,352 other food-handlers." The report notes that in the somewhat careful examination the findings were over four times more effective in bringing to light the presence of tuberculosis than in the method used on the large number examined routinely.

THE PRESENT SURVEY

The feeling has been current for some years that the method followed in the examination of food-handlers was open to question, both from the point of view of the effectiveness of the examinations made in finding communicable diseases, and also as to the scientific implications involved. It is of course open to considerable doubt whether there can ever be a sufficiently durational contact between the food-handler and the consumer of food to cause a transmission of tuberculosis or syphilis.

In July, 1932, we began a survey of one thousand apparently healthy food-handlers in New York City. Because of the much greater number of men than women included in the group of one thousand first surveyed, it was decided to continue the study to include two thousand food-handlers. An effort was made to keep the number of men and women of the second group of one thousand as equal as possible.

THE OBJECTIVE

The study was undertaken with two objectives in view:

1: To determine the incidence, extent and character of pulmonary-tuberculosis lesions in an average group of apparently healthy food-handlers.
2: To determine, if possible, what would be an effective way, in a community like New York City, to screen out those cases of tuberculosis in food-handlers which might prove important sources of infection with tubercle bacilli.

The yearly examination of food-handlers has been part of the supervisory function of the Health Department's Bureau of Preventable Diseases. By these examinations the Department has had an approach

to masses of apparently well adults of different racial and age-groups. In these groups, too, are found adults not differing in any apparent manner from other adults in similar nonhazardous industrial occupations. An epidemiological study of a group of such adults, comprising persons of varying nationalities with varying lengths of contact with tuberculosis, should give us valuable data, not only regarding the prevalence of tuberculosis among food-handlers, but, in addition, offer a field for the fruitful study of the incidence of tuberculosis in any adult industrial group not engaged in an extra-hazardous occupation.

THE PLAN

A plan of procedure was worked out in consultation with the appropriate officials of the Division of Tuberculosis, the Bureau of Preventable Diseases of the Department of Health, and the Secretary of the Industrial Hygiene Division of the New York Tuberculosis and Health Association.

Arrangement was made with the Physician-in-Charge of the Occupational Clinic in the Borough of the Bronx to refer to the Mott Haven Tuberculosis Clinic of that borough 10 cases each day for examination. All the individuals thus referred were taken at random from among the applicants for a food-handler's permit. Ten was fixed as the maximum number that could be handled effectively each day with the available equipment and personnel in the time allowed for the study.

THE EXAMINATION

At first our plan was to include in the examination:

1: The taking of a careful clinical history.
2: A thorough physical examination of the chest.
3: A roentgenogram of the chest.
4: The examination of the sputum.
5: An intracutaneous tuberculin test.

After examining the first 200 individuals by this method, we discovered that the findings on physical examination of the chest revealed very little that could be considered of importance in the diagnosis of these cases, as compared with the X-ray findings. The history, likewise, was found to be of very little help. For fear that it might prevent them from obtaining the desired permit, all subjects denied any previous illness in themselves or their families; it was thus impossible to obtain

any sufficiently accurate information to be of value in the study. The intracutaneous tuberculin test, interpreted according to the classification of the National Tuberculosis Association in its booklet, *Childhood Type of Tuberculosis*, was found to be positive to 0.1 mgm. of Old Tuberculin as prepared by the Health Department in 78 per cent of the cases, thus proving itself of no value in our effort to discover clinically active tuberculosis. (In this connection it is interesting to note that, notwithstanding the fact that the group comprised individuals between the ages of fifteen to seventy years, there were still 22 per cent who reacted negatively to 0.1 mgm. of Old Tuberculin by the intracutaneous method.)

We then modified our method of examination. To reveal tuberculous lesions in the lungs, we chose to make:

1: A routine roentgenogram of the chest.
2: An examination of the sputum.
3: A physical examination of the chest of those in whom a pulmonary lesion was demonstrated by the X-ray.

Our diagnosis of these cases was based principally upon changes noted in the roentgenograms. Appreciating the divergence of opinions regarding indefinite changes in the roentgenogram, no cases showing this characteristic of X-ray finding were included. Each of the positive cases, therefore, showed definite parenchymatous changes or definite calcified nodes. "Peribronchial infiltrations," "enlarged hilum shadows," were not considered in our interpretation of the X-ray films. All cases were excluded in which a definite tuberculous parenchymatous or lymphatic lesion could not be demonstrated to an experienced observer.

In our classification of the lesions, as demonstrated by the X-ray, we used the nomenclature of the National Tuberculosis Association, as described in *Diagnostic Standards* (ninth edition, 1931).

By "Active Tuberculosis" we designated all cases which showed:

1: A diffuse or circumscribed infiltration in the parenchyma of the lungs, or
2: Cases with numerous tuberculous lesions in one or both lungs.

"Latent adult tuberculosis" we called all cases with demonstrable parenchymatous lesions which were shown to be well healed by fibrosis or calcification.

"Healed childhood tuberculosis" we termed all cases of demonstrable tuberculous calcified primary foci and calcified tracheobronchial lymph nodes.

All the films have been read by Dr. Pessar. All the positive films were subsequently reread jointly by Drs. Martin and Pessar of the Division of Tuberculosis, Department of Health of the City of New York, and James Burns Amberson, Jr., Visiting Physician, Bellevue Hospital. Any questionable film about which there was disagreement or uncertainty has been called "negative." Thus, the personal factor in our interpretation was completely eliminated.

Of the first group of 1,000 cases examined, there were 772 men and 228 women. A study of these cases shows that there were 1,100 X-ray examinations and 1,100 routine sputum examinations. The total number of cases positively diagnosed was 125, all over fifteen years of age. As a consequence of the paucity of physical signs of pulmonary tuberculosis in these cases, no analysis of these are attempted in this study. Of the total of 125 positive diagnoses, 109 (87 per cent) had no diagnostic physical signs. The diagnosis was based principally upon changes noted in the roentgenogram. Of these cases 73 (59 per cent) were classified as "healed childhood tuberculosis"; 16 (13 per cent) as "latent adult tuberculosis"; and 36 (29 per cent) as "active pulmonary tuberculosis."

TABLE 1

Tuberculous lesions demonstrated by routine X-ray chest examinations of the first one thousand food-handlers

NUMBER OF PERSONS	HEALED CHILDHOOD	LATENT ADULT	ACTIVE TUBERCULOSIS	TOTAL X-RAY LESIONS
	per cent	*per cent*	*per cent*	*per cent*
Men, 772	59 (7.6)	14 (1.8)	30 (3.9)	103 (13.3)
Women, 228	14 (6.1)	2 (0.9)	6 (2.6)	22 (9.6)
Total...1,000	73 (7.3)	16 (1.6)	36 (3.6)	125 (12.5)

In the second group of 1,000 food-handlers examined, there were 473 men and 527 women. There was evidence of clinically active tuberculosis as demonstrated by the X-ray in 10 cases, as compared with 36 of the first group. There was evidence of latent adult tuberculosis in 19 cases, and evidence of healed childhood tuberculosis in 83 cases, as compared with 16 and 75 cases, respectively, of the first group. In spite, however, of these differences in the figures, and notwithstanding the fact that there was such a wide variation in the sex-distribution of the two groups studied, the average incidence of tuberculous X-ray lesions is approximately the same for both groups, not only in the total for the groups, but also in the percentage for the different types of lesions

according to our classifications. Thus, we find that the total incidence of the healed childhood type of lesion is 7.3 per cent in the first group where we had 772 men and 228 women, and 8.3 per cent in the second group of 473 men and 527 women. There was 1.6 per cent in the total of latent adult-type of lesions in the first group, and 1.9 per cent for the

TABLE 2

Tuberculous lesions demonstrated by routine X-ray chest examinations of the second thousand food-handlers

NUMBER OF PERSONS	HEALED CHILDHOOD		LATENT ADULT		ACTIVE TUBERCULOSIS		TOTAL X-RAY LESIONS	
		per cent		*per cent*		*per cent*		*per cent*
Men, 473	49	(10.3)	15	(3.2)	7	(1.5)	71	(15.0)
Women, 527	34	(6.4)	4	(0.8)	3	(0.6)	41	(7.8)
Total...1,000	83	(8.3)	19	(1.9)	10	(1.0)	112	(11.2)

TABLE 3

Composite table of tuberculous pulmonary X-ray lesions in two thousand food-handlers

NUMBER OF PERSONS	HEALED CHILDHOOD		LATENT ADULT		ACTIVE TUBERCULOSIS		TOTAL X-RAY LESIONS	
		per cent		*per cent*		*per cent*		*per cent*
Men, 1,245	108	(8.7)	29	(2.3)	37	(3.0)	174	(14.0)
Women, 755	48	(6.3)	6	(0.8)	9	(1.2)	63	(8.3)
Total...2,000	156	(7.8)	35	(1.7)	46	(2.3)	237	(11.8)

TABLE 4

Age-distribution—by color

AGE	WHITE	NEGRO	TOTALS
Under 20 years	274	7	281
20 to 29 years	575	35	610
30 to 39 years	491	26	517
40 to 49 years	391	13	404
50 to 59 years	160	2	162
60 years and over	25	0	25
Unknown	1		1
Totals	1,917	83	2,000

second group. Finally, in the average total of X-ray lesions found, there was 12.5 per cent in the first group and 11.2 per cent in the second group of one thousand examined.

An important difference, however, appears in the active-tuberculosis group. In this class we find an average total of 3.6 per cent for the

first group and only 1.0 per cent for the second group. Considering the fact that tuberculous pulmonary lesions are known to be more common in males than in females, and in view of the fact that the number of men examined in the first group was three times greater than the number of women in the same group, and that there was a slight predominance of women over men in the second group, it is reasonable to assume that the composite table 3, giving the average of the two groups as 2.3 per cent, represents the true situation in New York City. We are justified, then, in assuming that the average incidence of active pulmonary tuberculous lesions among food-handlers in New York City is approximately 2 per cent as shown in table 3.

DISCUSSION

Pathologists and clinicians have known for many years that the number of people with tuberculous lesions in the lungs is much greater than the number of those with active tuberculous disease. The presence of cicatrized or calcified tuberculous lesions, at necropsies of persons who have died of other diseases, is looked upon as an incidental finding.

With the universal use of X-rays for diagnostic purposes, it has been observed that in a decidedly noteworthy proportion of cases with active and progressive lesions no definite physical signs or clinical symptoms may be present.

It is true, as Dr. David A. Stewart says, that "Tuberculosis can be like an iceberg, only one-tenth visible and nine-tenths submerged."

The tremendous importance of these silent, invisible and submerged cases of active tuberculosis as carriers and potential sources of infection can readily be realized. They assume at once an important rôle in the problem of the prevention of tuberculous infection and disease.

However, we would indeed consider our efforts wasted were the results of this survey to reveal nothing more than the now generally known and universally accepted fact that, in urban communities, tuberculous pulmonary X-ray lesions are widespread, and that among these there are many cases of grave lesions in individuals who are apparently in good health. Our study derives its importance, and the results of the study assume great significance, when viewed from the standpoint of a community health problem.

There were 325,000 food handlers examined in New York City in one year. This estimate is based on Health Department records of examination of food-handlers by private physicians and Health Department clinics. This number does not include many thousands of food-handlers

who for one reason or another were not examined and reported upon to the Department of Health. If the 2 per cent shown by our survey represents the average incidence of active tuberculosis among the food-handling population of New York City, our local tuberculosis problem is indeed a difficult one. Evaluated in the light of facts revealed by our survey, it means that in New York City we have over 6,500 unknown, unobserved and uncontrolled cases of clinically active pulmonary tuberculosis, or 6,500 potential sources for the dissemination of tubercle bacilli. And what is the number of susceptible contacts to these uncontrolled cases?

Nor is this the whole story. New York City has been called the melting-pot. But, from the standpoint of tuberculosis, it is a pot full of variable susceptibles. The food-handling population of New York City represents the full gamut of tuberculosis susceptibility and resistance, including individuals of the Jewish and Italian peoples with their comparatively higher resistance, through the German, English, Irish and Swedish, down to the Mexican, Negro and Porto Ricans, with their extreme susceptibility and very low resistance. Viewed from this community aspect, the facts revealed by our survey assume immediately great significance, and present a definite and real problem in tuberculosis prevention and control for our public-health administrators.

CONCLUSIONS

1. Active tuberculous pulmonary lesions to the extent of approximately 2 per cent were found in apparently healthy food-handlers in New York City. We believe that this represents the average situation in all large urban communities. In New York City, with a food-handling population of more than 325,000 individuals, this percentage represents the existence of not less than 6,500 cases of unknown and therefore uncontrolled active pulmonary tuberculosis.

2. In addition, there is evidence of many thousands of cases of arrested tuberculosis, latent childhood tuberculosis and pleurisy among these food-handlers.

3. A good X-ray film is the most effective means for the successful demonstration of the existence of tuberculous pulmonary lesions. When the question of tuberculosis is involved, no physical examination of the chest is worth its name without the X-ray.

4. Active and progressive pulmonary tuberculosis may exist without demonstrable diagnostic physical signs.

THE VALUE OF THE NEGATIVE INTRACUTANEOUS TUBERCULIN (MANTOUX) TEST IN ADULTS[1]

M. R. LICHTENSTEIN

The intracutaneous tuberculin test as an aid in the diagnosis of adult patients with suspected tuberculosis has suffered almost complete neglect. In infancy and early childhood, it is generally agreed that the test is of preëminent importance.

In the adult a positive test is of very limited value, but a negative test in properly selected cases rules out tuberculosis. The latter concept has been propounded by Krause, Chadwick, Willis, and Hart, but is unknown or doubted by many. We wish to show here that the test has been of value to us in a certain number of the most difficult type of cases.

The reason for the neglect of the test in adults is found in the prevalent conceptions: first, that negative intracutaneous tests may occur in the presence of active tuberculosis; and, second, that practically all normal adults, especially in cities, give a positive intracutaneous test.

The first idea is erroneous, since it has been shown by D'Arcy Hart that all cases of pulmonary tuberculosis react if concentrations up to 1 to 10 are used. The only exceptions occurred in moribund patients, and these, as a rule, are not problems for diagnosis.

The second conception, that practically all normal adults are positive and that there is therefore no use in testing, is also fallacious. The number who are negative probably varies widely with the locality, but it is enough to make the test worth while, and is probably increasing because of the isolation of open cases.

Under what circumstances does a test for the exclusion of tuberculosis become of importance? The most difficult type of case for diagnosis is the suspected early pulmonary tuberculosis with negative sputum, dubious X-ray, and inconstant or slight physical findings. Such patients frequently enter sanatoria and undergo months of observation as a final effort toward diagnosis. If they have no tuberculosis they waste several months and occupy valuable space, to be told finally that they are ar-

[1] From the Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

rested cases, and leave with the stigma of tuberculosis and a perpetual dread of breaking down. The cases reported here have been mainly of the above class. No special effort was made to procure nontuberculous patients. They were sent in to the Municipal Tuberculosis Sanitarium of Chicago by the dispensary examining physicians as suspected cases in the usual manner. Any patients not proved to be tuberculous by the preliminary study and observation in the admission ward of the Sanitarium were referred for tuberculin test as doubtful cases. There were 162 such cases between March 1, 1932, and December 1, 1932.

Technique: The intracutaneous test was used; the quantity injected for each test was 0.05 cc.; readings were made at 48 hours; O.T. was used at first, and later T. P. T. (Seibert). Testing was begun with 1/100,000, 1/10,000 and 1/1,000 dilutions. If negative, the 1/100, and, after

TABLE 1

Intracutaneous tests on doubtful cases

Positive 1/100,000	8
Positive 1/10,000	55
Positive 1/1,000	76
Positive 1/100	3
Positive 1/10	5
Positive 1/1	1
Negative 1/1	14
Total	162

intervals of 48 hours each, if negative, the 1/10 and 1/1 or full-strength solutions were injected.

Results: In table 1 are indicated the number of patients opposite the weakest dilution to which they reacted. We are chiefly concerned with those who failed to react to the usual test dilution of 1/1,000. Fourteen, or 8.6 per cent, were completely insensitive to all tests. These could at once be ruled as nontuberculous. Nine, or 5.6 per cent, reacted to the stronger dilutions. The status of these patients remains in some degree doubtful, but it is strongly probable from our observations that they cannot have any *active* tuberculosis. Analysis of the complaints of the 23 hyposensitive patients is seen in table 2.

The only nonpulmonary case (not listed above) was a suspected tuberculous arthritis, completely insensitive to tuberculin, and proved nontuberculous on biopsy.

The definite exclusion of tuberculosis as a cause of the symptoms led

TABLE 2

Showing important data concerning 23 hyposensitive patients from a series of 162 suspected tuberculosis patients

PATIENT	SEX	AGE	COMPLAINT	DURATION OF ILLNESS	CONTACT WITH TUBERCULOSIS	FEVER	LOSS OF WEIGHT	COUGH	TIRED	PHYSICAL FINDINGS	SPUTUM	X-RAY	FINAL DIAGNOSIS	TUBERCULIN REACTION
							lbs.							
R. B.	F.	19	Cough, colds, loss of weight, night-sweats	10 months	0	0	0	+	+	Negative	1 positive, later found to be clerical error	Negative	Nontbc.; nonspecific laryngitis	Completely insensitive
A. G.	F.	26	Pain in chest, anorexia, fatigue, dysphagia	2 years	0	0	8	0	+	Negative	Negative	Negative	Psychoneurosis; globus hystericus	Completely insensitive
J. P.	M.	22	Colds, cough, expectoration, haemoptysis, tired, loss of weight	2 years	0	Occasional	12	+	+	Negative	Negative	Doubtful	Mitral stenosis; enlarged heart; nontbc.	Completely insensitive
A. S.	M.	19	Weak, tired	2 years	0	0	2	0	++	Negative	Negative	Negative	Nontbc. Probably due to rapid growth, —12 inches in 1 year	Completely insensitive
O. B.	M.	35	Cough, expectoration, night-sweats	3 months	0	0	16	+	+	Occasional râle	Negative	Negative	C.N.S. syphilis; Wassermann ++++	Completely insensitive
A. L.	F.	26	Cough, loss of weight, expectoration	12 years	0	0	15	+	+	Negative	Negative	Negative	Deprivation. Supposed to have tuberculosis 12 years ago. Had tuberculin injections for 1 year	Completely insensitive

K. C.	M.	27	Pain in right shoulder	2 months	0	0	13	0	0	Negative	Negative	Doubtful	Nontbc. joint; biopsy negative for Tbc.	Completely insensitive
C. W.	F.	29	Cough, fatigue, loss of weight	4 months	?	Occasional	12	+	+	Negative	Negative	Negative	Influenza and sequelae	Completely insensitive
L. B	M.	50	Cough, fatigue, loss of weight	5 years	0	Occasional	20	+	+	Râles in bases	Negative	Dubious	Mitral stenosis; lipiodol shows marked bronchiectasis	Completely insensitive
T. K.	F.	19	Cough, expectoration, pain	5 months	0	0	5	+	+	Negative	Negative	Negative	Thyrotoxicosis; BMR + 36	Completely insensitive
I. H.	F.	26	Cough, streaking, pains	2 years	+	99°	10	+	+	Negative	Negative	Negative	Psychoneurosis; endocervicitis	Completely insensitive
J. D.	M.	19	Cough, expectoration, streaking, night-sweats	3 months	0	0	5	+	+	Râles, right apex	Negative	Shadow, right apex	Unilateral apical bronchiectasis	Completely insensitive
E. R.	M.	23	Cough, expectoration, night-sweats, loss of weight	1 year	0	99²	?	+	+	Negative	1 positive before admission	Negative	Deprivation; bronchitis	Completely insensitive
M. A.	F.	21	Cough, tired, loss of weight	9 months	0	99°	10	Sl.	+	Inconstant râles, right apex	Negative	Negative	Pelvic infection	Completely insensitive
E. W.	F.	45	Tired, weak, night-sweats	3 months	0	0	12	0	+	Negative	Negative	Negative	Deprivation	Positive to 1/1 dilution
A. G.	F.	47	Cough, anorexia, emesis, expectoration	8 years	0	0	0	+	+	Râles, left base	1 positive 8 years ago	Bronchiectasis	Bronchiectasis	Positive to 1/10 dilution
D. D.	F.	35	Tired, anorexia, loss of weight	5 months	0	99⁴ to 101	22	+	+	Negative	Negative	Negative	Syphilis; Wassermann ++++	Positive to 1/10 dilution
B. M.	M.	46	Cough, expectoration, haemoptysis	5 years	0	Occasional	40	+	+	Occasional râles, apices	1 positive before admission	Negative	Repeated acute respiratory infections	Positive to 1/10 dilution

TABLE 2—*Concluded*

PATIENT	SEX	AGE	COMPLAINT	DURATION OF ILLNESS	CONTACT WITH TUBERCULOSIS	FEVER	LOSS OF WEIGHT	COUGH	TIRED	PHYSICAL FINDINGS	SPUTUM	X-RAY	FINAL DIAGNOSIS	TUBERCULIN REACTION
							lbs.							
J. K.	M.	27	Cough, tired, loss of weight	8 years	0	+	10 in 6 weeks	+	+++	Few râles	Negative	Negative	Chronic sinusitis; malingerer	Positive to 1/10 dilution
E. L.	F.	21	Cough, tired	1 year	+	0	0	+	+	Negative	Negative	Negative	Pelvic infection	Positive to 1/10 dilution
E. S.	F.	45	Cough, loss of weight, tired	4 months	0	0	36	+	+	Negative	Negative	Interlobar shadow	Acute pleuritis; chronic colitis	Positive to 1/100 dilution
M. A.	F.	25	Cough, loss of weight	1½ years	?	0	20	+	+	0	1 positive before admission	Negative	Thyrotoxicosis	Positive to 1/100 dilution
W. S.	M.	30	Cough, expectoration, tired, loss of weight, pain	6 years	0	101 occasionally	18	+	+	Occasion râles in apices	Negative	Negative	Bronchiectasis	Positive to 1/100 dilution

to intensive efforts to make a correct diagnosis. In most cases definite causes for the patients' complaints were found.

Table 2 shows the important data concerning each patient, including the final diagnosis. Four patients stated that they had had one positive sputum found before entrance. One of these was discovered later to be purely a clerical error. In the other three cases no data were available.

DISCUSSION

The fact that patients who are insensitive to tuberculin are thereby proved nontuberculous, with few exceptions, has been clouded by the finding that some tuberculous patients do not react. Hart has recently demonstrated in a large series of patients that practically all tuberculous patients react if the test is carried into the stronger concentrations. This we have corroborated in a similar series as yet unpublished. Those who fail to react fall in the group of moribund or highly toxic patients. Depressed sensitivity may also occur for a variable period after a contagious disease or a course of tuberculin therapy. The accumulation of evidence indicates that the negative intracutaneous test is very reliable in the absence of any of the above causes for depressed sensitivity. Hart established the percentage of possible error at about 2 per cent, this including the moribund patients. If these are excluded and only his pulmonary cases examined, the error approaches zero.

In view of the above we may well state that the negative intracutaneous test rules out tuberculosis with as much certainty as the finding of the organisms in the sputum rules it in. Both tests are thoroughly reliable if the technique and choice of patients is correct.

Complete insensitivity to tuberculin is generally held to mean that the patient has never had a primary infection, although some believe that after complete healing of the primary lesion the skin may again become insensitive. The patients who give positive reactions to the strong concentrations (1/100, 1/10 and 1/1) have evidently had a primary infection at some time, and may even have had active tuberculosis in the past. We can feel reasonably sure that such patients have no *active* tuberculosis, provided they are not moribund or very ill. Chadwick and Willis assert that tuberculosis is ruled out if the patient fails to react to the 1/100 dilution. The above is intended to apply to pulmonary, but not to other tuberculosis. Skin tuberculosis of certain types is said by some to have regularly a depressed sensitivity.

It may of course be true that the majority of adult suspects will have

a positive intracutaneous test. There can be no question, however, that the number of adults who are negative is considerable among patients seen in private practice, and that the range of usefulness of the test is therefore correspondingly increased.

That every effort should be made to weed out all nontuberculous patients as soon as possible is apparent. It conserves space in the institution; it removes the stigma of a dreaded disease; and it aids in making the correct diagnosis. Every means available needs to be used, even though it helps in only a small percentage of cases. It is demonstrated in this series of cases that the tuberculin test, carried into the stronger concentrations, is of real value.

Two main groups of patients present themselves as problems in diagnosis. First is the group with symptoms suggestive of early tuberculosis, but with negative or dubious physical and X-ray findings. Second is the group with physical findings or X-ray shadows and with few or no symptoms. Most of the patients in our tuberculin-insensitive series who came under the first heading were finally diagnosed as showing various sequelae of acute pulmonary infections, or subacute infections of other organs. Under the second heading most of the cases turned out to be bronchiectasis or cardiac disease. One of the latter group was an asymptomatic unilateral apical bronchiectasis sent in with a diagnosis of tuberculosis because of the apical râles and X-ray shadow. Although many of the patients discussed here were suspected to be nontuberculous on clinical grounds, the clinching argument in *proving* them nontuberculous was the tuberculin test. Without the test a period of observation, probably of several months' duration, would have been necessary before the clinician could safely state that the patient had no tuberculosis. During this interval, contact with open cases would be a source of grave potential danger to the insensitive patient.

The field of usefulness of the test is probably restricted in large cities. However, the fact that it is of some help even in a tuberculosis sanatorium makes it evident that it must be of considerable value in private practice and in less densely populated places, where the percentage of tuberculin-insensitive individuals is greater.

The test is helpful precisely in those cases in which diagnosis is most difficult, namely, the early doubtful cases. Occasionally it solves quickly and decisively a problem in diagnosis which would never be solved otherwise. It should be a part of the routine of everyone who considers tuberculosis.

SUMMARY

1. Complete insensitivity to tuberculoprotein makes it certain that the patient is nontuberculous, with the few exceptions given.

2. Complete insensitivity is found in a sufficient number of adults to make the test worth while.

3. Patients who react only to the strong concentrations of tuberculoprotein, with the same exceptions, almost certainly have no *active* tuberculosis.

4. The test quickly excludes as nontuberculous a number of suspects, including some of the most difficult cases for diagnosis.

5. The intracutaneous test, carried into the stronger concentrations, should be a part of the diagnostic routine of every physician considering tuberculosis.

REFERENCES

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(2) HART, P. D'ARCY: The value of tuberculin tests in man, Medical Research Council, 1932, Special Report 164.

THE CORRECTED SEDIMENTATION RATE (*C. S. R.*) IN PULMONARY TUBERCULOSIS[1]

An Analysis of Approximately 250 Cases[1]

SAMUEL FRIEDMAN

Since 1918, when Fahraeus (1) rediscovered the phenomenon of blood sedimentation, a great many publications, devoted to this subject, have been written. The value of the blood-sedimentation test as an aid in the study of cases of pulmonary tuberculosis has been demonstrated frequently. In spite of this plethora of literature, it was felt, because previous methods had been so varied and nonuniform and results expressed in so many different units, that an analytical study, using the latest and undoubtedly the best technique, might not be amiss.

The sedimentation phenomenon is a nonspecific reaction of uncoagulated blood, manifesting itself by differences in the rapidity with which red blood cells sediment, being much slower in health than in disease. The sedimentation test consists of observing the speed with which the red blood cells settle out from the plasma.

Previously, three principal methods, each with its many modifications, have been developed for performing the test. These are, briefly, as follows:

1: The Distance Method: This method is the oldest, and was first advocated by Fahraeus, but the Westergren (2) modification is the one most commonly used. Briefly, the test consists of noting the distance through which red cells sediment, by reading the height of the supernatant plasma at definite intervals: namely, one hour, two hours, and twenty-four hours.

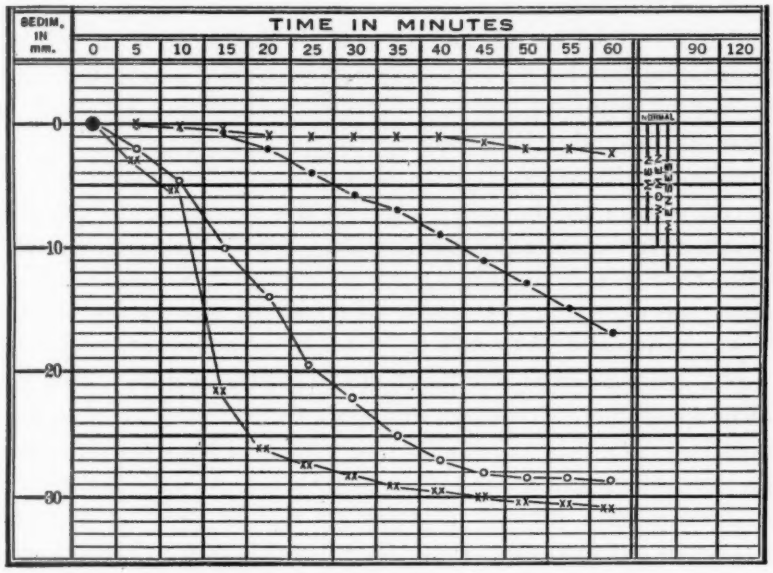
2: The Time Method: This was first advocated by Linzenmeier (3) and is called the *Linzenmeier method.* The principle here is to note the time it takes for the red cells to sediment to a given distance.

Thus, in the distance method, one fixes the time and measures the distance, recording the result in millimetres; while, in the time method, one fixes the distance and observes the time, recording the result in

[1] From the Essex Sanatorium, Middleton, Massachusetts.

minutes. In each method, there is only one variable, either time or distance.

3: The Graphic Method: This method, developed especially by Cutler (4) (5) (6) in this country, combines the principal features of both the time and distance methods, and, by using both variables, expresses the actual velocity or rate of sedimentation of the red cells. The method consists of recording



GRAPH 1. Taken from CUTLER, J., *Am. J. M. Sc., 1926, clxxi, 882*

——×——×—— Horizontal line (clinically healthy individual).
——●——●—— Diagonal line (clinically quiescent tuberculosis).
——○——○—— Diagonal curve (clinically slightly active tuberculosis).
——××——×× Vertical curve (clinically markedly active tuberculosis).

the distance through which the red cells sediment at frequent intervals of time, that is, every five minutes, for one hour, and then charting the results in the form of a graph, using sedimentation in millimetres as ordinates, and time in minutes as abscissae. Cutler recognizes four distinct types of graphs as demonstrated in graph 1 herewith.

As may be readily seen, this is a great improvement over the first two methods which show us only one phase of the reaction—the end-result—and do not give a true picture as to the actual velocity of sedimentation.

However, the outstanding objection to previous methods has been

the failure to correct the values obtained for variations in red-blood-cell volume. It has been shown that by diminishing the number of particles in a suspension, the mean free path of such particles becomes greater and consequently the rate at which the particles settle is increased. So, in blood, the sedimentation rate is inversely proportional to the erythrocytic cell volume, other factors being the same. To put it simply, the fewer the red cells, or the smaller the red-cell volume, the more quickly the cells will sediment and *vice versa*, other things being equal. Obviously, in diseases like tuberculosis and rheumatic fever, in which the sedimentation test has had its widest use, anaemia is common, and the red-blood-cell volume becomes a definite variable and correction for it becomes of increasing importance.

Rourke and Ernstene (7) have shown how sedimentation rates vary with cell volume and have corrected for this variation, arriving at what they called the "corrected sedimentation index." At this point, we will describe their technique, as it is the one we used in this study.

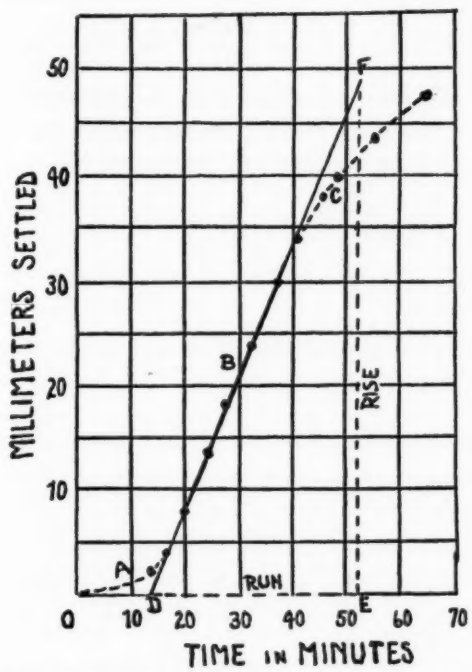
Tubes are used similar to those described by Rourke and Plass (8), with a capacity of 1.20 to 1.25 cc., a height of 100 mm., and graduated in 2-mm. divisions, from 0 at the top to 100 at the bottom. Two or 3 cc. of blood are drawn, without venous stasis, into a syringe and transferred immediately to a tube containing 1 or 2 mgm. of heparin. (Rourke and Plass have shown that other anticoagulants slow the sedimentation rate.) The blood is then allowed to stand for a short time (at least fifteen minutes and not more than three hours) until it assumes room temperature. The specimen is then thoroughly shaken so as to ensure a uniform suspension. The sedimentation tube is filled to the zero mark, and the degree of settling is recorded at frequent intervals (every five or ten minutes), until two successive readings indicate a decreased rate because of "packing." The sedimentation tube is then transferred to a centrifuge and spun at 3,000 r.p.m. for thirty minutes, thus obtaining the haematocrit. We now plot the time-distance readings, with the millimetres of settling of blood cells as ordinates, and time in minutes as abscissae, obtaining the curve shown in graph 2 as an example.

The typical curve has three phases as shown by Rothe (9):

1: The preagglutination phase, or period of aggregation;
2: The agglutination phase, or period of constant sedimentation;
3: The packing phase;

represented, respectively, by sections *A*, *B*, and *C* in the above curve. It is this second phase or period of constant sedimentation that represents

the true velocity. The slope of the straight-line portion (B) of the curve is calculated in the following manner: The determined straight line (section B) is extended below to the base-line at point D and upward to any convenient point F. A perpendicular FE is dropped from point F to the base-line at point E. The slope of the line is then $\frac{\text{Rise}}{\text{Run}}$ or $\frac{FE}{DE}$, which expresses the uncorrected sedimentation rate in millimetres per minute. We now proceed to correct this sedimentation rate for any



GRAPH 2. Taken from ROURKE AND ERNSTENE, *J. Clin. Invest., 1930, viii, 545*
For description see text

variance that it may have from the normal haematocrit or cell-volume percentage. Rourke and Ernstene have taken 45 as the standard red-blood-cell volume percentage or haematocrit reading, and, by removing portions of red blood cells, have constructed curves showing how the sedimentation rate varies with the haematocrit. By consulting the chart which they have made, the uncorrected sedimentation rate of any specimen of heparinized blood with an haematocrit reading between 20 and 55 volumes per cent of cells can be transposed to the rate which would have been obtained had the specimen contained 45 volumes per

cent of cells, thus arriving at the "corrected sedimentation index," expressed in millimetres per minute. We have called this the *corrected sedimentation rate* (hereafter referred to as *C.S.R.*) to avoid confusion with Cutler's "sedimentation index."

We followed the above technique closely in obtaining the *C.S.R.* in approximately 250 cases of pulmonary tuberculosis. With few exceptions, two determinations were made simultaneously on the same blood and the average was taken as the final determination. Blood from female patients was taken only during the intermenstrual period. Rourke and Ernstene (7) have chosen 0.35 $\frac{\text{mm.}}{\text{min.}}$ as the upper normal limit for the *C.S.R.* Because of some previous work in rheumatic fever and this present study, we believe we can raise our upper limit slightly to 0.40 mm. per min., and have classified our determinations as follows:

Normal *C.S.R.*..... up to 0.40 mm. per min.
Moderately elevated *C.S.R.*.....0.40 to 0.60 mm. per min.
Elevated *C.S.R.*..... 0.60 to 0.90 mm. per min.
Greatly elevated *C.S.R.*..... over 0.90 mm. per min.

We will now proceed to analyze the results obtained and see how they compare with various clinical findings.

1: Clinical Classification: At this sanatorium, patients are classified clinically into nine groups ranging from class 1, the strictly bed-patients, to class 9, comprising patients almost ready for discharge. In order not to make the analysis too complicated, we have put classes 1, 2 and 3 in one group, classes 4, 5 and 6 in a second group, and classes 7, 8 and 9 in a third group. The correlation between the *C.S.R.* and the clinical classification is seen in table 1.

TABLE 1

GROUP	TOTAL NUMBER	C.S.R.							
		Normal		0.40 to 0.60		0.60 to 0.90		Over 0.90	
Males:									
Classes 1, 2, 3.....	42	0	0%	2	5−%	8	19+%	32	76+%
Classes 4, 5, 6.....	47	18	38+%	5	10+%	8	17%	16	34%
Classes 7, 8, 9.....	38	17	45−%	10	26+%	4	10+%	7	18+%
Females:									
Classes 1, 2, 3.....	54	7	13−%	13	24+%	13	24+%	21	40−%
Classes 4, 5, 6.....	49	19	39−%	10	20+%	10	20+%	10	20+%
Classes 7, 8, 9.....	16	8	50%	5	31+%	3	19−%	0	0%

The figures in table 1 are practically self-explanatory. It will be noticed that among the female patients there are seven in classes 1, 2 and 3 with normal *C.S.R.* and that the percentages in the greatly elevated zone of *C.S.R.* are lower for the females than for the males. We will find throughout this study that the female patients have lower rates than the males. We believe this to be due to several factors: (1) female patients are as a rule less sick on entry; and (2) the female patients are kept in the lower classes longer than are the males and consequently show less activity, class for class, than do the males. Of the 7 female patients in classes 1, 2 and 3 with normal *C.S.R.*, five were cases receiving artificial-pneumothorax therapy and one was a thoracoplasty case, but we shall discuss this later.

The average *C.S.R.* of the various classes follows:

Male:

Classes 1, 2, 3	1.22 mm. per min.
Classes 4, 5, 6	0.67 mm. per min.
Classes 7, 8, 9	0.57 mm. per min.

Female:

Classes 1, 2, 3	0.83 mm. per min.
Classes 4, 5, 6	0.55 mm. per min.
Classes 7, 8, 9	0.42 mm. per min.

This again tends to show that the female patients were, in general, less sick and had less activity than the male patients.

We can readily see, then, that the *C.S.R.* and the clinical classification correspond well. The first group, comprising classes 1, 2 and 3, which contain practically bed-patients only, has the highest average *C.S.R.*, the highest percentages in the greatly elevated zone, and practically no patients in the normal zone. (There are no male patients in the normal zone, and, excluding those receiving or having received collapse therapy, only one female patient of this group in the normal zone.) The third group, comprising classes 7, 8 and 9, which contain patients that are quiescent and almost ready for discharge, has the lowest percentages in the greatly elevated zone, the highest percentages in the normal zone, and the lowest average *C.S.R.* The second group, comprising classes 4, 5 and 6, which are intermediary in clinical activity, shows the same middle course in terms of *C.S.R.* We believe that the *C.S.R.*, repeated at regular intervals, should form an important factor in the clinical promotion of patients.

2: Sputum: Cutler (4) found no relationship between the sedimentation rate and the presence or absence of tubercle bacilli in the sputum. We have analyzed the *C.S.R.s* obtained, with respect to positive or negative sputum. (We have called sputum negative if it has been so for at least six months.) These findings are recorded in table 2.

TABLE 2

SPUTUM	TOTAL NUMBER	C.S.R.							
		Normal		0.40 to 0.60		0.60 to 0.90		Over 0.90	
Males:									
Positive	80	12	15%	7	9−%	14	17+%	47	59−%
Negative	53	27	51−%	8	15+%	10	19+%	8	15+%
Females:									
Positive	56	10	18−%	9	16%	15	26+%	22	40−%
Negative	64	23	36−%	21	33+%	12	18+%	8	12+%

It can be readily seen that there is a distinct difference in *C.S.R.* between patients having positive and those having negative sputum. Those with negative sputum show a much higher percentage of normal *C.S.R.* and a much lower percentage in the greatly elevated zone than those with positive sputum. In other words, in terms of the *C.S.R.*, tuberculous activity and positive sputum are more frequently found together than are tuberculous activity and negative sputum, and the corollary is also true. Can this be demonstrated clinically, also? We again analyzed the patients with positive or negative sputum from the standpoint of clinical classification and found the correlation to be seen in table 3.

TABLE 3

GROUP	TOTAL NUMBER	SPUTUM			
		Positive		Negative	
Males:					
Classes 1, 2, 3	39	34	87%	5	13%
Classes 4, 5, 6	48	30	62+%	18	38−%
Classes 7, 8, 9	39	15	38+%	24	62−%
Females:					
Classes 1, 2, 3	56	38	68%	18	32%
Classes 4, 5, 6	48	17	35+%	31	64+%
Classes 7, 8, 9	16	0	0%	16	100%

Although tables 2 and 3 are not directly comparable, we see basically the same idea expressed, clinically, in table 3 as we did in table 2 in

terms of *C.S.R.*; namely, that tuberculous activity and positive sputum are more frequently found together than are activity and negative sputum.

3: Râles: We next analyzed the *C.S.R.* with respect to the absence or presence of râles. We classified patients into three groups, as follows:

1: No râles present (0 râles)
2: Few râles present, usually localized to apex (f râles)
3: Fairly numerous or numerous râles present (+ râles)

The results obtained are shown in table 4.

TABLE 4

RÂLES	TOTAL NUMBER	C.S.R.							
		Normal		0.40 to 0.60		0.60 to 0.90		Over 0.90	
Males:									
+	58	7	12+%	3	5+%	14	24+%	34	59−%
f	32	9	28+%	10	31+%	2	6+%	11	35−%
0	42	22	52+%	3	8−%	7	16+%	10	24−%
Females:									
+	35	5	14+%	4	11+%	12	34+%	14	40−%
f	36	9	25%	10	28−%	6	17−%	11	30+%
0	45	18	40+%	14	31+%	8	18−%	5	11+%

The figures in table 4 need little comment. Patients without râles have the highest percentage of normal *C.S.R.* and the lowest percentage of greatly elevated *C.S.R.*; those with numerous râles have the highest percentage of greatly elevated *C.S.R.* and the lowest percentage of normal *C.S.R.*; while those with few râles hold an intermediary position.

In a correlation of râles with clinical classification, as was done previously with sputum, we find the results in table 5.

TABLE 5

GROUP	TOTAL NUMBER	0 RÂLES		f RÂLES		+ RÂLES	
Males:							
Classes 1, 2, 3.....	42	6	14+%	7	16+%	29	69−%
Classes 4, 5, 6.....	48	17	35+%	10	22−%	21	43%
Classes 7, 8, 9.....	39	17	43+%	14	36+%	8	20%
Females:							
Classes 1, 2, 3.....	53	15	28−%	14	26+%	24	46−%
Classes 4, 5, 6.....	48	20	42−%	20	42−%	8	17+%
Classes 7, 8, 9.....	16	9	56+%	3	19−%	4	25% (?)

Here, again, we see that the clinical classification shows the same correlation with respect to the presence or absence of râles as did the *C.S.R.*, save for a slight deviation in the last female group, where the numerical total is so small as to introduce chances for percentage error. We may say, then, that both from the standpoint of the clinical classification and the *C.S.R.*, patients with râles are more apt to have activity than patients without râles.

4: Temperature: Patients were divided into the following groups with respect to temperature.

1: Flat temperature for at least the past two months
2: Infrequent slight rise in temperature, not more than 99.5°
3: Frequent rise in temperature or continuous temperature.

The comparison between these groups and the *C.S.R.* is seen in table 6.

TABLE 6

TEMPERATURE	TOTAL NUMBER	C.S.R.							
		Normal		0.40 to 0.60		0.60 to 0.90		Over 0.90	
Males:									
Without fever	76	35	46+%	12	15+%	10	13%	19	35+%
Infrequent 99°+	16	1	6+%	1	6+%	6	37+%	8	50%
Frequent rise or continuous fever	33	1	3%	0	0%	5	15%	27	82%
Females:									
Without fever	71	27	38+%	21	30−%	14	20−%	9	12+%
Infrequent 99°+	26	7	27−%	4	15+%	6	23+%	9	35−%
Frequent rise or continuous fever	23	0	0%	3	13%	9	39+%	11	48−%

It will be seen that there is one patient in the third group with a normal *C.S.R.* This is undoubtedly only a temporary fall and subsequent determinations revealed an elevated rate. It is in the cases without fever that the *C.S.R.* will prove to be of the greatest value, for here we are without any definite clinical aids as to activity. It is in these cases that the *C.S.R.* serves as the only precise guide as to the measure of activity.

5: Duration of Disease: Cutler (4) found no relation between the duration of the disease and the sedimentation test. We have likewise

found no definite correlation between the *C.S.R.* and the duration of the disease, as determined from the onset of symptoms. At first glance, this might seem contrary to expectation, for one would think that older cases would be less active than recent ones. However, patients, on entry to a sanatorium, are practically all active, although not equally so, regardless of whether the infection is recent, or old and reactivated. In other words, a patient, who may have had the disease for ten years in a quiescent stage and is suddenly reactivated, enters a sanatorium, where, obviously, he shows the same activity as a patient who may have had the disease for only six months. The patients were divided into four groups with respect to duration of disease:

1: One year or under
2: 1–4 years
3: 5–9 years
4: 10 years and over

The comparison between duration of disease and *C.S.R.* is seen in table 7.

TABLE 7

DURATION	TOTAL NUMBER	C.S.R.							
		Normal		0.40 to 0.60		0.60 to 0.90		Over 0.90	
Males:									
One year or under.....	27	4	15−%	6	22+%	6	22+%	11	41%
1–4 years.....	58	19	32+%	5	9−%	10	17+%	24	41%
5–9 years.....	27	9	33+%	1	4−%	3	11+%	14	51+%
10 years and over.....	15	3	20%	2	13+%	5	33+%	5	33+%
Females:									
One year or under.....	16	3	19−%	5	31+%	4	25%	4	25%
1–4 years.....	61	17	28−%	10	16+%	18	30−%	16	26+%
5–9 years.....	25	6	24%	7	28%	7	28%	5	20%
10 years and over.....	10	3	30%	5	50%	0	0%	2	20%

As may be seen in table 7, there is practically no relationship between the total duration of the disease and the *C.S.R.*

6: Weight: We will now proceed to analyze the *C.S.R.* with respect to loss or gain in weight. Patients were divided into the following four groups:

1: Gained more than 20% of admission weight
2: Gained 10–20% of admission weight

3: Gained less than 10% of admission weight
4: Lost or failed to gain

The comparison between gain in weight and *C.S.R.* is seen in table 8.

TABLE 8

CHANGE IN WEIGHT	TOTAL NUMBER	C.S.R.			
		Normal	0.40 to 0.60	0.60 to 0.90	Over 0.90
Males:					
Gain of 20% or more.....	27	8 30−%	5 18+%	5 18+%	9 33+%
Gain of 10–20%.....	26	14 54−%	2 8−%	6 23%	4 15+%
Gain of less than 10%....	31	11 35+%	8 26−%	2 6+%	10 32−%
Failed to gain or lost.....	33	0 0%	0 0%	8 24+%	25 75+%
Females:					
Gain of 20% or more.....	19	6 31+%	5 26+%	5 26+%	3 16−%
Gain of 10–20%.....	33	7 21+%	11 33+%	6 18+%	9 27+%
Gain of less than 10%....	37	12 32+%	5 14−%	11 30−%	9 24+%
Failed to gain or lost.....	18	4 22+%	2 11+%	4 22+%	8 44+%

Although patients who had been at the sanatorium only a short time were excluded from the weight study, we admit that comparisons are difficult because of wide differences in the length of time that patients had been at the sanatorium. However, we believe that we can definitely conclude that failure to gain weight or loss of weight most commonly means presence of activity (this is especially striking among males), but that gain in weight need not mean cessation of activity. We have seen the same correlation in previous studies in rheumatic fever. Thus, the *C.S.R.* may serve here as a warning beacon while the weight chart might lull us into a sense of false security.

7: Complications: We should naturally expect cases with complications to have a higher average *C.S.R.* than uncomplicated cases. This was found to be true. We found 29 cases with major complications, 26 being tuberculous complications and the other 3 not connected with the disease, as follows: enteritis 7, laryngitis 4, enteritis and laryngitis 4, enteritis and arthritis 1, draining sinuses 4, empyema 2, keratitis 1, abscess 1, tuberculous meningitis 1, draining cervical lymph nodes 1, pregnancy 1, and syphilis 2. The average *C.S.R.* was 1.33 mm. per min. and the range from 0.83 to 2.05 (the highest rate recorded). The percentage analysis follows:

	number	*normal*	*0.40 to 0.60*	*0.60 to 0.90*	*over 0.90*
Cases with complications..	29	0 0%	0 0%	5 17+%	24 83−%

8: Artificial Pneumothorax: The *C.S.R.* in cases receiving artificial-pneumothorax therapy was next analyzed. The result may be seen in the following table:

	total number	*normal*	*0.40 to 0.60*	*0.60 to 0.90*	*over 0.90*
Pneumothorax cases—male..	16	4 25%	2 12.5%	6 37.5%	4 25%
Pneumothorax cases—female.	40	17 42.5%	7 17.5%	10 25%	6 15%

In the males, the figures are not striking, differing practically not at all from the percentages in general. However, the number is too small to be able to draw definite conclusions therefrom. The average *C.S.R.* of male pneumothorax cases was, moreover, lower than the average *C.S.R.* of the rest of the patients, being 0.69 mm. per min. for the pneumothorax cases and 0.82 mm. per min. for the general average.

Female cases receiving artificial-pneumothorax therapy, however, show definite improvement over the average case with respect to the *C.S.R.* The pneumothorax cases have 42.5 per cent in the normal zone of *C.S.R.*, whereas, in general, there were only 30 per cent in the normal zone, while the pneumothorax cases have only 15 per cent in the greatly elevated zone of the *C.S.R.*, whereas in general there were 26 per cent in the greatly elevated zone. The average *C.S.R.* of female patients in general was 0.66 mm. per min. (in the elevated zone), and that of the female pneumothorax cases was 0.55 mm. per min. (in the moderately elevated zone). As we have noted before, five of the seven female patients in classes 1, 2 and 3 with normal *C.S.R.* are pneumothorax cases.

9: Thoracoplasty: There were 8 cases, all females, on whom thoracoplasty had been performed. These thoracoplasties had all been done within the past two and a half years. The average *C.S.R.* in these cases was 0.42 mm. per min. The highest *C.S.R.* was but 0.57 mm. per min. The percentage analysis was:

	total number	*normal*	*0.40 to 0.60*	*0.60 to 0.90*	*over 0.90*
Thoracoplasties.....	8	2 25%	6 75%	0 0%	0 0%

Although the number of cases is small, these figures tend to show that thoracoplasty is the most efficient form of collapse therapy for curbing tuberculous activity.

10: As an Aid in Diagnosis: During the course of this study, there were 5 patients admitted to the sanatorium and discharged in a short time as nontuberculous. The *C.S.R.* in these cases was respectively: 0.23, 0.25, 0.18, 0.10 and 0.25. There were also 3 patients in the sana-

torium upon whom the diagnosis of tuberculosis could not be definitely settled. The *C.S.R.* in these cases was 0.17, 0.30 and 0.19. There were 2 cases with recent history of pleurisy with effusion as the only sign of tuberculosis. The *C.S.R.* in these cases was 0.52 and 0.56 (moderately elevated). We admit that this is too small a series from which to draw definite conclusions, but we feel that the *C.S.R.* may well be of distinct aid in establishing a diagnosis in doubtful cases. Cases of pleurisy with effusion can, we believe, be followed with special advantage by means of the *C.S.R.*, for in these cases other signs and symptoms are lacking.

11: Haematocrits: We thought it would be interesting, finally, to consider and analyze the haematocrit values obtained. We divided the haematocrits into four groups: (1) 45 and over, (2) 40–45, (3) 35–40, and (4) under 35. As might be expected, the male patients had higher haematocrits, on the whole, than the female patients. This is seen numerically as follows:

Hematocrit	*males*	*females*
over 45	49	5
40–45	51	58
35–40	25	45
under 35	7	13

The lowest haematocrit obtained was 28 (this patient died in a few weeks), and the highest was 55.5 (this patient did not have tuberculosis). We found that the sickest patients, as a rule, had the lowest haematocrits. When we compared haematocrit values (which show us the presence or absence of anaemia) with the *C.S.R.*, we obtained the values shown in table 9.

TABLE 9

HAEMATOCRIT	TOTAL NUMBER	C.S.R.							
		Normal		0.40 to 0.60		0.60 to 0.90		Over 0.90	
Males:									
45 and over	49	19	39−%	8	16+%	7	14+%	15	30+%
40–45	51	20	39+%	5	10−%	7	14−%	19	37+%
35–40	25	0	0%	2	8%	5	20%	18	72%
under 35	7	0	0%	0	0%	2	29−%	5	71+%
Females:									
45 and over	5	0	0%	3	60%	0	0%	2	40%
40–45	58	22	38−%	10	17+%	18	31%	8	14−%
35–40	45	12	26+%	13	29−%	5	11+%	15	33+%
under 35	13	1	8−%	1	8−%	5	38+%	6	46+%

Due to the fact that females have normally somewhat lower haematocrits, the figures for them are not as striking as for the males. Among the latter, we see strikingly that those patients who are anaemic, that is, have haematocrits lower than 40, have far more tuberculous activity than those with normal haematocrits. Thus, of the male patients with haematocrits lower than 40, not one had a normal *C.S.R.*

COMMENT

We feel strongly that the sedimentation test reported by means of the *C.S.R.* should become a most important aid in the management of a case of pulmonary tuberculosis. It is a reliable index of activity, and, what is more important, serves as an index when other phenomena, such as the temperature and the weight-curve, cease to be of value. Rarely, a single determination may be in error, but in following cases of such chronic nature as tuberculosis or rheumatic fever, in which the sedimentation test has proved of greatest value, the test is naturally repeated at definite intervals, so that any error may be easily discounted by subsequent determinations. The *C.S.R.*, we believe, repeated regularly, is certainly of far more aid in determining the actual decrease or increase of pathological activity than is the X-ray picture, in which changes denoting softening or calcification as representing changes in activity or healing are far more difficult to interpret. Yet, repeated X-rays are a routine at practically all sanatoria, whereas the sedimentation test has been greatly neglected. The *C.S.R.* cannot tell us, as does the X-ray if the disease has spread anatomically, but can and does tell us, in quantitative terms, if the disease has spread in pathological activity. We believe that, in a convalescent patient, when we have so little otherwise to guide us, the *C.S.R.* is the most important single piece of information in judging the progress of the case. It should also form an important aid in arriving at a diagnosis in early and doubtful cases. It is not of value in a differential diagnosis between tuberculosis and other lung conditions, such as carcinoma, which also cause increased *C.S.R.*

SUMMARY

1. The corrected sedimentation rate (*C.S.R.*), arrived at by the Rourke and Ernstene method, gives the most accurate data in the study of blood-sedimentation rates and should be the method of choice in further investigations.

2. Approximately 250 cases of pulmonary tuberculosis are analyzed from the standpoint of the *C.S.R.*

3. The grouping of patients according to their *C.S.R.* agrees well with their clinical classification.

4. Tuberculous activity, as measured by both the *C.S.R.* and the clinical classification, and positive sputum are more frequently found together than are activity and negative sputum.

5. Patients without râles have less activity, as measured by both the *C.S.R.* and the clinical classification, than patients with râles.

6. Patients without fever may or may not have an elevated *C.S.R.*, depending on the amount of latent activity. Patients with fever almost invariably have an elevated *C.S.R.*

7. There is no correlation between the duration of the disease of the patients in this sanatorium and the *C.S.R.*

8. Gain in weight may or may not be associated with a normal *C.S.R.*, depending upon the amount of latent activity. Loss of weight is almost always associated with an elevated *C.S.R.*

9. Patients with complications show the highest *C.S.R.*

10. Patients receiving artificial-pneumothorax therapy show a somewhat lower average *C.S.R.* than do the other patients. Female patients receiving artificial pneumothorax show a distinctly greater percentage of normal *C.S.R.*

11. Patients with thoracoplasty have a definitely lower average *C.S.R.*

12. The *C.S.R.* proved to be of aid in the differential diagnosis of early and doubtful cases, being normal in all those cases that were discharged as nontuberculous.

13. Haematocrit values were higher in male patients than in female patients. Patients with low haematocrits had a much greater percentage of elevated *C.S.R.* than those with normal haematocrits.

14. A more widespread use, in sanatoria, of the sedimentation test reported by means of the *C.S.R.* is urged.

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A SIMPLIFIED TECHNIQUE FOR BLOOD-SEDIMENTATION INDICES[1]

L. D. VAN ANTWERP

Many modifications of the sedimentation-index test have been brought out since Fahraeus's work in 1918 (1). But all depend for their results, as did his, on some method of determining the rate of fall of the erythrocytes in the blood-plasma following the addition of an anticoagulant. The test, itself, is considered of real merit by many clinicians, especially in the fields of tuberculosis and abdominal surgery, but unfortunately it has still remained somewhat too involved for use by most men in private practice or in institutions with limited laboratory facilities.

With these ideas in mind, we have evolved a modification of the Cutler technique which requires a minimum of apparatus, of preliminary preparation, and of observations after the test is started. For these reasons it may be of use to the profession.

The more important and most widely used modifications of this test are those of Westergren, of Linzenmeier and of Cutler. In the Westergren and Cutler methods the index is determined by the fall in millimetres of the column of erythrocytes in a given period of time; in the Linzenmeier method it is determined by the time necessary for the column to fall a predetermined distance. Thus, in the first two methods the time is the fixed factor; in the third, the distance is fixed. The Westergren method consists of drawing the citrate into the syringe, adding the blood drawn from a vein, mixing both in a storage tube, filling a special pipette from the storage tube, and placing it in a special rack for observation (2). The Linzenmeier method consists of fewer steps but requires continual observation in determining the elapsed time for the column to fall to the mark; this time may be as long as six, twelve or even twenty-four hours. In the most used of the Cutler methods 0.1 cc. of 3 per cent solution of sodium citrate is mixed in a 2-cc. syringe with 0.9 cc. of blood and emptied into a special 1-cc. tube. These tubes are of such diameter that the blood column to the zero mark is approximately 5 cm in length, although Cutler makes no special point of this fact; and the

[1] Read at a conference of the Connecticut State Tuberculosis Commission, Meriden, Connecticut, January 16, 1933.

tube is calibrated from zero downward in millimetres. Readings are made every five minutes for an hour, and these readings are plotted on a special chart, resulting in a curve of the fall of the column. Conclusions are drawn both from the total fall of the column in an hour's time and from the shape of the curve obtained (4)

We believe the Cutler method to be the most practical of all the three methods, but we found that, to determine a series of ten to twenty-five indices at one time, as is often necessary, there was required a very considerable number of tubes, mixing chambers, and syringes with the incidental sterilization procedure. It occurred to us that, if a syringe could be made with markings corresponding to those found on the sedimentation tubes, we might use the barrel of the syringe as the tubes themselves are used, and thus simplify the technique. We then found that a standard syringe which had met certain requirements could be used instead of a special one.

In reviewing the literature, we found that Fahraeus attempted to simplify his own technique and at the same time decrease the amount of blood required by the use of a very small graduated syringe which he filled with a small amount of citrate and a drop of blood, hanging the syringe in a rack and reading it in twenty minutes by a small millimetre scale held beside the barrel (5). However, Fahraeus has discarded this method as impracticable, and the present writer understands that Cutler has also discarded his own micromethod. Our technique makes use of a syringe as did Fahraeus, though our observations were complete before his work was brought to our attention.

A 2-cc. *Vim Emerald Syringe*,[2] in which the blood-column is exactly 5 cm. high, was selected. This, of course, is the same as the height of the column in the Cutler method. We then compared our technique with his, using identical bloods drawn at the same time, and found the two ran nearly parallel,—near enough that we were convinced that we might use the Cutler standards on the results obtained by our own technique. We read our results in percentages instead of millimetres, but these are directly transposable with the Cutler standards by multiplying his figures by two, since each millimetre on his 50-mm. tube represents 2 per cent of the total column. (See table 1.) The fact that we used twice as much blood as Cutler does did not influence the results; he obtains nearly identical curves in 5-cc. and 1-cc. tubes provided that the height of the column is the same in both.

[2] The syringe, as specified, may be obtained from the MacGregor Instrument Company, Needham, Massachusetts.

TABLE 1

Comparison of our indices with adjusted Cutler indices

SUBJECT NUMBER	SEX	CUTLER INDEX	ADJUSTED CUTLER INDEX (×2)	OUR INDEX
5	M	1.5	3	4
13	M	2	4	4
12	M	2.8	5.6	5
22	M	4	8	8
21	F	5	10	10
20	F	6.5	13	13
9	M	8	16	15
6	M	8	16	16
14	M	8	16	16
1,087	M	8.8	17.6	16
1,799	M	8	16	16
7	M	9	18	17
10	M	8.5	17	17
24	F	9	18	17
27	F	9.1	18.2	18
15	M	11	22	23
25	F	12	24	24
26	F	12	24	24
28	F	17.8	35.6	38

(For explanation of table, see text.)

TABLE 2

Determination of normal standards

MALE		FEMALE	
Subject number	Sedimentation index	Subject number	Sedimentation index
3	2	21	10
4	2	19	11
2	4	20	13
5	4	18	13
13	4	17	15
23	4	24	17
12	5	27	18
8	6	16	22
22	8		
1	11		
11	11		
9	15		
6	16		
14	16		
7	17		
10	17		

Note: This short series was considered sufficient because of the close checking with the Cutler standards. (Female: 10 mm. (20 per cent). Male: 8 mm. (16 per cent) (4).)

On a short series of tests done on apparently normal individuals, we found normal one-hour readings to compare very closely with his. We have adopted 20 per cent as the upper limit of normal for women and 16 per cent for men. (Cutler's normals are 10 and 8 mm. respectively (4).) (See table 2.)

TABLE 3

Determination of the influence of air contact on the sedimentation rate

SUBJECT NUMBER	SEX	INDEX OPEN	INDEX CLOSED
9	M	15	15
10	M	15	15
13	M	4	4
14	M	16	16
22	M	8	8
23	M	4	4
1,799	M	16	16
19	F	11	11
20	F	13	13
21	F	10	10
24	F	17	17
25	F	24	24
26	F	24	24
27	F	18	18
28	F	38	38
1	M	10	11
4	M	3	2
5	M	5	4
6	M	17	16
8	M	5	6
12	M	6	5
15	M	22	23
1,087	M	17	16
29	F	48	47
2,230	F	69	68
2	M	6	4
3	M	4	2
17	F	17	15

Note: In order to determine the influence of air contact on the rate of sedimentation, tests were made on identical bloods simultaneously, using one syringe with the plunger in place and the barrel only of a second one.

It occurred to us that the absence of air-contact in the closed syringe might influence the rate of sedimentation, but a series of determinations on identical bloods, run simultaneously in open and closed syringes, convinced us that this factor does not materially influence the rate of fall, and probably not at all. (See table 3.)

TECHNIQUE USED

The technique of our modification is as follows: 0.2 cc. of a sterile 3 per cent solution of sodium citrate is drawn from a serum bottle under sterile technique. The needle is then removed from the serum-bottle cap and, following a venous puncture from a suitable vein, the syringe is filled to the 2-cc. mark with blood, and removed from the vein. A bubble of air is then drawn through the needle into the syringe and, by carefully inverting this several times, the blood and citrate are mixed. The bubble is then expelled, the needle removed and replaced by a cap, and the capped syringe placed in a test-tube rack for observation. Our caps were made by breaking the needle from a discarded hypodermic needle and filling the perforation with paraffin. A 24-gauge, 1-inch needle seems best suited for use in the test.

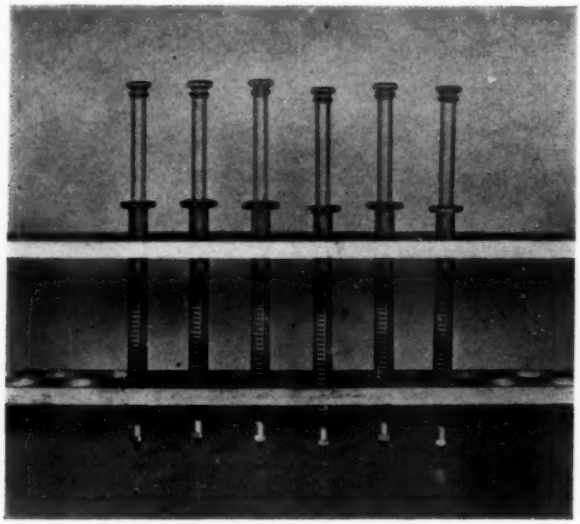

FIG. 1. THE AUTHOR'S TECHNIQUE IN USE

Our readings, at the present time, are limited to a single one taken at the end of one hour, since we have not been able to obtain any additional information by the use of the curve plotted from the five-minute readings, nor have we observed any advantage in readings taken beyond the one-hour interval, as in the Westergren method.

The advantages of this simplified technique may be considered as follows: The elimination of one or more steps in the determination of the index materially reduces the time necessary for the procedure. The small amount of blood necessary (1.8 cc.) allows the use of a small hypodermic needle, which causes a

minimum of discomfort to the patient and facilitates entrace to the small veins of children. A minimum of equipment is necessary and, once the syringe (which can be put to other uses in the private office) is acquired, the apparatus can be found in any physician's office, with the exception of the sterile citrate solution. The sterilization necessarily preparatory to the test is no more than is required for ordinary venipuncture. The index is determined by a single reading at the end of an hour, the apparatus requiring no attention during this time.

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THE LINZENMEIER BLOOD-SEDIMENTATION TIME IN TUBERCULOUS CHILDREN[1]

WILLIAM ANTHONY REILLY

The red-blood-cell sedimentation rate (the measurement from the top of the column of plasma to the upper level of cells in a given time) and the sedimentation time (the time required for cells to settle to a given depth) have been frequently studied in tuberculosis. The Linzenmeier method for sedimentation time has many advantages but has seldom been employed in this country. Hille (1) and Lederer (2) have established Linzenmeier sedimentation times for normal children.

Repeated observations of sedimentation time have demonstrated its diagnostic and more valuable prognostic advantages in tuberculosis. This is particularly valuable for clinicians confronted with the problems of the common type of tuberculosis in children, the so-called hilum-lymph-node lesion.

The Linzenmeier method is carried out as follows: 0.8 cc. of venous blood is drawn into a syringe containing 0.2 cc. of 5 per cent sodium citrate. After inverting the syringe, the mixture is introduced into a glass tube of 4-mm. diameter with an 18-mm. mark below the level of the 1-cc. volume. The time taken for the cells to sediment to the 18-mm. mark is noted. This procedure is easily and quickly done and the required apparatus is simple. The normal time, variable with age, is as follows:

0–2 months: May be as high as 10 hours
2 months–2 years: About 1½ hours
2 years–4 years: About 2½ to 3½ hours
5 years–6 years: About 2 hours
After 6 years: Time gradually rises until after 10 years, when females have a time of 4 to 6 hours and males 6 to 8 hours. After the 6th year a time under 2 hours is always pathological.

These results have been checked by the author.

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INTERPRETATION OF THE RED-BLOOD-CELL SEDIMENTATION

The settling of red blood cells in the blood *in vitro* is thought to be dependent mainly on certain protein constituents, fibrinogen and globulin. As these increase, sedimentation occurs more quickly. There are other controlling factors which are not well understood; for instance, the electrolyte content of plasma, the water content and temperature. These favor adhesion of the red cells and *rouleaux* formation. Toxins also accelerate sedimentation. The various bacteria do not cause enough difference in the sedimentation time as to be of differential diagnostic significance. While the sedimentation time is shortened in tuberculosis, this is not pathognomonic for that disease. Tuberculous disease having been diagnosed previously, the clinician will find the test more valuable in prognosis. As the sedimentation time becomes more nearly that of the normal child, the prognosis is much more favorable, since the patient is probably building sufficient immunity to combat the disease. The prognostic value of sedimentation is, therefore, more definite than in diagnosis in the common forms of childhood tuberculosis. It is probably as significant as any other laboratory method in evaluating the condition of the child.

The shortened sedimentation time will often disclose activity when temperature, weight, blood-cells and sputum do not reveal abnormality. Still more reliable in following activity are the roentgenogram changes, though these are known to evolve slowly. Yet, during this period a shortened sedimentation time is more easily and quickly obtained, and is evidence of activity.

RESULTS IN PATIENTS STUDIED

This study comprised 104 tests carried out on 36 tuberculous girls between the ages of 8 months and 14 years, from October, 1930, to March, 1931. Total white-blood-cell counts on fixed smears with Wright's stain and on supervitally-stained smears (the latter for observing monocytes) were done at times for correlation and comparison.

The hilar lesion in its active stages, presumably in the hilum lymph nodes, was generally accompanied by a shortened sedimentation time. This was true in 22 of 23 such patients. The most rapid times, however, occurred in the blood of those children with more active lesions than are usually found in the hilar lymph nodes. It was thus when cavitation of the lung (2 patients) or miliary tuberculosis existed. Almost as rapid

times were observed in patients with other disseminations, such as developing Pott's disease (2 patients) and the so-called allergic phenomena, phlyctenular keratoconjunctivitis (2 patients) and pleural effusions (2 patients). Occasionally, however, almost as short sedimentation times were found in the blood of children with hilar lesions.

Of the 33 patients considered clinically active, this was confirmed in 31 patients by a shorter sedimentation time. The remaining two patients had normal or longer times.

Compared or correlated with other laboratory tests for tuberculous activity, the sedimentation time indicated pathological effects much more frequently. Taking 6,000 to 12,000 as the normal range of total white blood cells, there were only rare increases in these children, whereas the Linzenmeier test always gave a rapid sedimentation time.

It is maintained that monocytes frequently increase in the blood of patients with tuberculous activity (3). The sedimentation time shows a consistent shortening. In 20 comparisons, the ratio of monocytes to lymphocytes did not indicate activity, whereas the sedimentation time was rapid in all 20 of these. Only once in 40 comparisons made on 23 patients did the ratio indicate activity and the sedimentation time fail to do so.

CONCLUSIONS

The Linzenmeier red-blood-cell sedimentation time done on 36 tuberculous girls 104 times was found to be a more reliable procedure in the prognosis than in the diagnosis of tuberculous activity. It is also of presumptive aid in diagnosing activity. The author believes it has an advantage over the usual signs, symptoms, and laboratory procedures in determining activity.

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THE EARLY DIAGNOSIS OF POTT'S DISEASE[1]

R. I. HARRIS

The early diagnosis of Pott's disease is of extreme importance, since it permits the early establishment of treatment. Other things being equal, the earlier efficient treatment is established the greater the prospect of cure, and the smaller the amount of permanent disability. In order that an early diagnosis may be reached it is necessary that the earliest symptoms of the disease be detected. The diagnosis of Pott's disease is obvious when a kyphosis is present, but this only appears after a considerable amount of destruction and collapse of vertebral bodies has occurred, and hence appears relatively late. It should be our aim to recognize the disease before the appearance of deformity. A unique opportunity to do this exists in those cases which develop while in sanatoria for the treatment of pulmonary tuberculosis. The constant supervision to which such patients are subjected provides an excellent chance to detect spinal disease in its earliest phases if only we will be sufficiently alert to appreciate the significance of these earliest symptoms.

EVOLUTION OF POTT'S DISEASE

It will simplify the picture if we review briefly some important points in the evolution of Pott's disease. Every case of spinal tuberculosis is a secondary focus arising because tubercle bacilli have been deposited in the vertebrae from the blood-stream. Haematogenous implantation is the only mode of infection. This, of necessity, implies that the patient has at least one other active focus of tuberculosis (the primary focus) from which the blood-stream has been infected. In the majority of patients with Pott's disease it is possible to detect this primary focus. Usually it is in the lung, but it may be in any of the situations through which tubercle bacilli enter the body, or it may even happen that another haematogenous focus can give rise to tuberculous septicaemia, which in turn may cause Pott's disease. Sometimes the primary focus is difficult or impossible to detect. There are many obvious reasons for this. The

[1] Read at a session of the Clinical Section at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 28, 1933.

primary focus may be small and so situated as to give rise to no symptoms; for example, intestinal tuberculosis with mesenteric adenitis. Again, we may be dealing with a spinal lesion laid down at a time so far distant in the past that the primary focus from which it arose is now healed and unrecognizable.

Every lesion of spinal tuberculosis, therefore, is evidence that the blood-stream has been invaded by tubercle bacilli. Occasionally, we can actually recover tubercle bacilli from blood cultures. With the able assistance of my colleague, Dr. R. M. Price, I have three times secured positive blood-cultures from patients suffering from bone-and-joint tuberculosis. It is strange that tuberculous septicaemia is not more frequently demonstrated. One undoubted reason is that the attempt to recover them is seldom made. Since Pott's disease means present or past tuberculous septicaemia, it would not be strange to find other foci of tuberculous disease of haematogenous origin. This is actually the case. About half the patients with spinal tuberculosis will display one or more other foci in the spine, or foci in other bones and joints, or else in the kidneys and urinary tract. The high incidence of renal tuberculosis amongst patients suffering from bone-and-joint disease is of particular interest and significance. In one series of 43 adult patients, tubercle bacilli were recovered from the urine of 37 per cent.

We may summarize the situation as follows: Every case of tuberculosis, wheresoever the lesion may be situated, may develop Pott's disease by means of the blood-stream. This is especially true of pulmonary tuberculosis, since most cases of Pott's disease arise from primary pulmonary foci. Every case of Pott's disease at some time has had a tuberculous septicaemia. Many cases of Pott's disease have other haematogenous foci either in bones or joints or in the kidneys.

PATHOLOGY OF POTT'S DISEASE

Once implanted in the vertebral body, the tubercle bacilli set up a characteristic reaction leading to the production of tubercles and a tuberculous osteitis. This is essentially a destructive process, in which the bone is slowly absorbed and replaced by tuberculous granulation tissue. As cartilage is singularly susceptible to the attack of tubercle bacilli, the intervertebral disks in the vicinity of the focus are rapidly destroyed. As a rule the disease starts on the upper or lower surface of a vertebral body, spreads across the intervertebral disk and involves the adjacent surface of the next body. The pathological lesion in the early

stage, therefore, consists of destruction of the adjacent surfaces of two vertebral bodies together with the intervening intervertebral disk. For a very long period of time, destructive processes predominate. Only late is there any evidence of new bone-formation, and then frequently it is small in amount.

SYMPTOMS

The pathological process in Pott's disease gives rise to a group of distinctive symptoms which may be summarized as follows:

Pain of a distinctive character,
Muscle spasm with resulting limitation of movement,
Deformity,
Abscess-formation, distinctive for the segment of the spine in which the disease occurs,
Characteristic radiographic appearances,
Paraplegia in a few cases.

Pain: The earliest symptom of Pott's disease is pain. The intensity of this pain varies with the duration of the disease, the activity with which it is progressing, and the amount of destruction of vertebral bodies which has occurred. Broadly speaking, the longer the disease has existed (provided treatment has not been started), the more active the infection and the greater the amount of destruction of bone, the greater will be the pain. In the diagnosis of Pott's disease in its earliest stage, therefore, we need not expect to find a great deal of pain. Indeed, in some cases it is so mild as to amount only to discomfort. The pain of Pott's disease has certain distinctive features by which, as a rule, we can recognize its nature. It is situated in one or both of two locations: either in the back at the level of the disease (local pain), or else in the trunk in segments which correspond in level to the diseased area (referred pain). Frequently the referred pain only is present and if it is limited to one side of the trunk, it may lead to serious errors in diagnosis; for instance, appendicitis, or renal stone instead of Pott's disease. Like all pain of spinal origin it is intensified by activity and weight-bearing, and is relieved by rest. This is its most distinctive feature and should be emphasized, since it distinguishes spinal pain from all forms of visceral pain with which it might be confused. If the patient does not relate the fact spontaneously, it can always be elicited by judicious questioning that standing, walking, working, lifting, and stooping make his pain

worse, while lying down, flat and still, relieves it. Moreover, certain kinds of activity are particularly prone to exaggerate the pain, and of these the explosive expiratory acts such as coughing and sneezing are especially productive of great increase in pain. Frequently, the patient will say spontaneously, "to sneeze is agonizing." Again, any activity or movement which suddenly increases the weight borne by the diseased area, such as occurs in stepping down steps or riding in a jolting car, enhances the pain. It is necessary in the early stages of Pott's disease to pay attention to these distinctive features, because the pain does not become disabling in intensity until the disease is much more advanced. In the early stage, the pain, though slight, is persistent, or at any rate recurs with every period of activity. As the disease progresses, the pain becomes more intense and more easily elicited by movement and is less readily relieved by rest. Because of the distinctive intensification of the pain by movement and weight-bearing, the patient learns instinctively certain characteristic mannerisms. When he sits down he carefully eases himself into the chair with his hands supporting the upper part of his trunk. He walks in a manner which avoids jarring.

Muscle Spasm: Pain arising from lesions in the musculoskeletal system gives rise to reflexes which increase the tone in muscles controlling the diseased part. Pott's disease is no exception to this rule. A focus of spinal tuberculosis is accompanied by spasm of the sacrospinal muscles in the segment affected by the disease and for a considerable distance above and below it. As a result of this muscle spasm, movement of the diseased segment is reduced. The patient experiences this as stiffness, and his doctor appreciates the absence of movement in the involved segment when he examines the back. To casual observation, this limitation of movement may not be obvious, since the patient learns to compensate for it. He may still be able to touch the floor without bending his knees but he does so by bending from the hips and not by bending his spine. Moreover, such movement is performed carefully because of pain.

Deformity: The characteristic deformity (kyphosis) results from destruction and collapse of the vertebral bodies, and hence can only occur when the disease has been present for a length of time sufficient to cause appreciable destruction. In the dorsal segment of the spine it appears much sooner than in the lumbar, the difference being due to the nature of the normal spinal curves. The lumbar spine normally curves forward in a well marked lordosis. Destruction and collapse of vertebral bodies

by tuberculosis in this region will cause, first, diminution in the curve of the normal lordosis, then complete flattening of the lumbar spine, and, finally, when great collapse of vertebral bodies occurs, the lumbar spine actually angulates backwards. The appearance of the characteristic kyphosis in the lumbar spine, therefore, indicates considerable destruction of vertebral bodies and is evidence of long-standing disease. In this region, long before kyphosis actually appears, the keen eye will have appreciated the diminution in normal lumbar lordosis which must first occur when the anterior support of the spine is diminished. In the dorsal region on the other hand, the normal curve is backward. The smallest amount of collapse of the dorsal vertebral bodies evidences itself as a small kyphosis. Deformity appears here much earlier than in the lumbar spine, though here too the disease must have existed for a length of time sufficient to cause body destruction. Every case of Pott's disease has had spinal tuberculosis for a considerable length of time before deformity appears. An observant physician will make the diagnosis in the pre-gibbus stage. Certainly, the absence of a kyphosis should not be regarded as indisputable proof against spinal tuberculosis.

Abscess: Nearly every case of Pott's disease is accompanied at some stage by an abscess. The situations in which such abscesses appear vary with the segment of the spine involved in the disease, but each segment is associated with a very distinctive type of abscess. To begin with, the abscesses which accompany Pott's disease have all the characteristics of tuberculous abscesses elsewhere. They increase in size slowly but steadily, often reaching a very large size. They are not very tender and the inflammatory reaction they excite is small, so small that they are designated "cold abscesses." They tend to spread in a definite anatomical fashion, dependent upon the spinal segment in which they originate. Abscess accompanying Pott's disease of the cervical spine collects beneath the deep layer of the cervical fascia and bulges forward into the pharynx as a retropharyngeal abscess. As it grows larger it may rupture spontaneously into the mouth or may spread laterally, to appear in the posterior triangle of the neck. Abscess accompanying dorsal Pott's disease collects in the mediastinum. It cannot be detected on physical examination because it does not bulge externally, but presents a characteristic shadow in X-ray, a fusiform opacity surrounding the involved segment. Abscess accompanying Pott's disease of the 12th dorsal vertebra frequently enters the *quadratus lumborum* muscle and, passing through Petit's triangle, appears in the loin as a lumbar abscess.

Abscess arising from lumbar Pott's disease enters the psoas muscle and, after filling the lower quadrant of the abdomen, passes with the muscle below Poupart's ligament and appears in the thigh. A psoas abscess is easily detected, not only by palpation, but also because it causes a characteristic disturbance of function of the psoas muscle. The great accumulation of pus within the psoas sheath makes complete extension of the thigh impossible. The hip remains partially flexed, though no movement other than extension is limited.

Two features about the abscesses with Pott's disease require to be emphasized. First, they must not be treated as an ordinary abscess by simple incision and drainage. To do so invites secondary infection and death from amyloid disease. Second, they frequently provide an easy means of confirming the diagnosis of tuberculosis. Examination of the pus removed by aspiration will usually reveal the presence of tubercle bacilli, though guinea-pig inoculation may be necessary for this proof.

Radiographic Changes: Radiography is a most important aid in the diagnosis of Pott's disease. Stereoscopic radiographs in the antero-posterior plane are of great value but good lateral radiographs are of much greater value. No attempt at the diagnosis of spinal tuberculosis should be made without good lateral radiographs. The changes seen in Pott's disease are very characteristic and can be briefly summarized. In the early stage, with which we are at present concerned, the disease is evidenced by destructive changes involving the adjacent surfaces of two vertebral bodies and the intervening intervertebral disk. The superior surface of one body will be eroded and destroyed. The intervertebral disk above it will be thin, and the inferior surface of the body above will be similarly destroyed. Frequently, in the adult, the destructive lesion never extends beyond this stage, but, in some adults, and frequently in children, the final amount of destruction is much greater. One or more vertebral bodies may be completely or nearly completely destroyed and the intervertebral disks between them completely absorbed. As the disease becomes older active destruction of bone ceases. The healing phase is characterized by new bone-formation, which may succeed in fusing the remnants of the diseased bodies into a single pyramidal mass. This represents the final stage of healing.

Paraplegia: Paraplegia, though it is an infrequent complication of Pott's disease and usually appears after the deformity, may sometimes be a very early sign, and, therefore, is worthy of mention here. It

almost always is a complication of upper dorsal Pott's disease. It is due, not to the severity of the deformity, but to the protrusion from the involved bodies, backward into the spinal canal, of a mass of inflammatory tuberculous material. Hence, it may appear without any accompanying kyphosis. This is rare. Very frequently however, indeed usually, it disappears without any change in the severity of the kyphosis. As the disease subsides, the tuberculous mass is absorbed and pressure on the cord is relieved. The earliest evidences, if the patient is still up and about, are difficulty in walking, frequent stumbling, and incoordinate movements of the legs. Sensory disturbances are rare, and bladder and rectal involvement occur only in the severe cases.

SUMMARY

1. Pott's disease, being haematogenous in origin, appears only in patients who have tuberculosis elsewhere. Though not a common disease, it is a potential possibility in every patient under treatment for tuberculosis.

2. It frequently is accompanied by other tuberculous lesions also of haematogenous origin in other parts of the spine, in the joints or in the kidneys.

3. Early treatment is so important that every effort should be made to recognize the disease in its earliest stages. The symptoms of patients in sanatoria should be carefully analyzed with this diagnosis in mind.

4. The symptom most valuable for early diagnosis is spinal pain, increased by activity and weight-bearing, and relieved by rest, experienced not only in the diseased area but referred also to spinal segments corresponding in level to the diseased vertebrae.

5. The remaining symptoms upon which a diagnosis may be made are muscle spasm, deformity, abscess-formation, characteristic radiographic appearance, and paraplegia.

6. The disease exists for a varying period of time before deformity appears, dependent partly upon the segment of the spine involved, but partly also upon the severity of the infection and the rapidity of its progress. Diagnosis in this period is difficult but important.

RESULTS IN 70 CONSECUTIVE CASES OF TUBERCULOUS EMPYEMA[1,2]

JOHN C. JONES AND JOHN ALEXANDER

It is not unusual to hear sanatorium physicians say that in their experience the mortality in the mixed tuberculous and pyogenic type of empyema has been between 90 and 100 per cent and that they have never had a patient who became genuinely cured. It is our impression that the majority of phthisiotherapists limit their treatment of tuberculous empyema, regardless of its type, to aspiration, and use closed or open drainage only when a prolonged trial of aspiration has failed and the patient is desperately ill. It is our thesis in this article that the successful management of tuberculous empyema demands the use of one or more of several procedures and that the treatment of each patient must be highly individualized.

Even when the various useful therapeutic measures have been used it is obvious that the results reported by different clinics will differ according as the mild or grave type of empyema has predominated among their patients. Relatively few authors give a clear statement as to the partition of their patients among the different types of the disease. We have collected the results in 779 cases from nineteen articles, fifteen of which have appeared since 1927. Of these 779 patients, 25.5 per cent were cured, 7.6 per cent were greatly improved and 13.9 per cent improved; 9.6 per cent were unchanged or could not be traced, 1.8 per cent became worse and 41.6 per cent died.

We have recently traced every one of the 70 consecutive patients who had been admitted to the Department of Surgery at the University of Michigan Hospital between January, 1927, and January, 1933. The results in these patients are: Cured, 54.3 per cent; improved, 8.5 per cent; not improved or worse, 4.3 per cent; dead, 32.9 per cent. By "cured" we mean that the empyema cavity is completely obliterated and that no sinus remains and that, if pulmonary tuberculosis was

[1] From the Department of Surgery, University of Michigan, Ann Arbor, Michigan.

[2] Read at a session of the Clinical Section at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 28, 1933.

present, sputum is now absent or it contains no tubercle bacilli. All of the patients listed as improved are still under treatment.

In table 1 the 70 cases are divided into groups according to the excellent classification of Hedblom. It will be seen that the tuberculous empyema was complicated at the time of admission by mixed pyogenic infection or by active pulmonary tuberculosis, or by both, in 69 of 70 patients, while seventeen had bronchopleural fistula. With the exception of the small series of Muralt and Weiller (*Rev. de la Tuberc., 1931, xii (3rd series), 172–179*) in which six cures and three deaths were reported

TABLE 1

Results, all groups, 70 cases

GROUP	NUMBER OF CASES	CURED	IMPROVED	WORSE OR NOT IMPROVED	DIED	DEATHS			
						No operation	Directly due to operation	Possibly indirectly due to operation	Not due to operation
1	1				1			1	
2	14	11	2		1				1
3	25	17		1	7	3	1	3	3
4	30	10 (12*)	4 (2*)	2	14	3	1		7
Total.....	70	38 (40*)	6 (4*)	3	23	6	2	4	11
Per cent...		54.3 (57.2*)	8.5 (5.6*)	4.3	32.9	8.5	2.9	5.7	15.8

Groups 1 and 2 had no demonstrable pulmonary tuberculosis; groups 3 and 4 had clinically active pulmonary tuberculosis, usually cavernous; groups 1 and 3 had pure tuberculous empyema; groups 2 and 4 had mixed tuberculous and pyogenic empyema.

* See asterisk footnote to table 4.

among 9 cases (in three of which tubercle bacilli were not demonstrated in the pleural fluid), repeated aspirations and continuation of the pneumothorax having been the only direct treatment, our results are, so far as we know, the best that have been reported. For this reason we believe that an analysis of our cases may be of interest.

The empyema was definitely proved to be tuberculous in 65 of our 70 cases by finding tubercle bacilli in the aspirated fluid or by direct smear, culture or guinea-pig inoculation, or by finding characteristic tubercles microscopically in a portion of the parietal pleural scar that was routinely removed for examination in those cases which we openly

drained. The 5 cases in which tuberculous empyema was not absolutely proved belong to group 3, which consists of pure tuberculous empyema with associated active pulmonary tuberculosis. Our records do not show that tubercle bacilli were demonstrated in the aspirated pus from these 5 cases, but in all of them the empyema complicated pneumothorax that was induced for cavernous pulmonary tuberculosis with tubercle bacilli in the sputum; we consider that the presumption that these 5 empyemata were tuberculous is virtually conclusive.

Thirty-eight of the patients were males and thirty-two, females. Thirty-nine of the 70 patients were between twenty and twenty-nine years of age. Three were younger than ten years of age, one being four, and three were older than fifty, one being sixty-three. Twenty-eight of the 70 empyemata resulted as a complication of induced pneumothorax, nineteen of these cases belonging to group 3 and nine to group 4. Sixteen of them have been cured, two are improved, two are not improved or are worse, and eight are dead. Of the 8 patients who died, two were too ill for anything but aspiration, four were too ill for anything more than drainage with or without phrenicectomy, and two had thoracoplasty.

Group 1 comprises the relatively unusual cases of pure tuberculous empyema without complicating pyogenic infection and without evidence of active pulmonary tuberculosis. The purpose of treatment in these cases is to bring about expansion of the lung with consequent obliteration of the empyema cavity. This should be accomplished by repeated aspirations, perhaps with temporary partial air replacement and virtually never by closed or open drainage because of the almost certain addition of pyogenic infection to the empyema. Extrapleural thoracoplasty should be performed only in the event that a reasonably prolonged trial of aspiration should fail to result in complete expansion of the lung, but not in every such case if the quantity of pus is stationary and if the patient is asymptomatic.

Our only group-1 patient was a boy of ten years of age with a history of empyema of four and a half months' duration. At the time of admission to the hospital there was no clinical or roentgenological evidence of pulmonary tuberculosis; the patient was severely toxic, and the aspirated pus thick and green. The boy appeared to be suffering from an acute pyogenic and nontuberculous empyema, and an associate in the clinic broke an absolute rule and openly drained the empyema without waiting first to determine whether or not pyogenic organisms could be demonstrated by smear or culture. The empyema cavity had a capacity

of 200 cc. and a routinely-removed specimen of the parietal pleural scar showed miliary tubercles. The patient continued his downhill course and died ten weeks later.

Group 2 consists of patients with mixed tuberculous and pyogenic empyema, but without evidence of active pulmonary tuberculosis. The object of treatment is to evacuate the pus because of its content of pyogenic organisms and to expand the lung so as to obliterate the empyema cavity. These objects may occasionally be accomplished by repeated aspirations with or without irrigations or instillations of dyes, gomenol or other chemical substances. As prolonged use of aspiration is likely to be both ineffectual and dangerous because of the associated pyogenic infection, closed or preferably open drainage usually becomes necessary. A phrenicectomy is useful to assist in obliteration of the

TABLE 2

Group 2, 14 cases: tuberculous and pyogenic empyema without active pulmonary tuberculosis

LAST OPERATION	NUMBER OF CASES	CURED	IMPROVED	UNIMPROVED	DIED
Open drainage	4	3			1*
Extrapleural or/and Schede thoracoplasty	10	8	2		
Total	14	11	2		1
Per cent		78.5	14.3		7.2

* Improved by drainage but general condition contraindicated thoracoplasty. Died three years after operation at the age of sixty-six from complications of marked hypertension.

empyema cavity, and this should be performed early, so as to cause a rise of the hemidiaphragm before it has become fixed by a rigid pleural scar. If aspiration, drainage and phrenicectomy fail to close the empyema completely and if the open cavity finally shows no disposition toward progressive closure, an extrapleural thoracoplasty and painting of the costal periosteum with 10 per cent formalin is the treatment of choice. Should a residual cavity remain several months after the extrapleural thoracoplasty it may be obliterated by a one- or more-staged Schede thoracoplasty. In group 2, as in all other groups, such general measures as bed-rest, a high caloric diet, heliotherapy, codliver oil, ferrum reductum and blood transfusion are used as indicated.

The results in our 14 group-2 patients are given in table 2, partitioned according to the last operation that it was necessary to use. Every one of the patients in this group came to us with a draining sinus of an

average of 2.3 years' duration,—a sinus which followed drainage elsewhere. We estimate that certainly not more than 15 per cent, and probably fewer, of these patients had a pyogenic infection complicating their tuberculous empyema before the initial drainage was performed, and that the great majority of the pyogenic infections that were present when we first saw the patients of this group were directly brought about by the mistake of draining a purely tuberculous empyema. The diagnosis of tuberculosis was first made at the University Hospital in 92.9 per cent of the 14 patients. In those patients in groups 2 and 4 whose empyemic pus we cultured, the following pyogenic organisms were found, singly or in combination: *Streptococcus haemolyticus, nonhaemolyticus, viridans,* and unclassified; *Staphylococcus aureus, albus,* and unclassified; pneumonocci; *Bacillus coli.*

Eighty-five and seven-tenths per cent of the 14 patients in this group had inadequate drainage at the time of admission, and reoperation for adequate drainage was therefore necessary. Three patients had tuberculosis of the ribs or cartilages; one is now cured and two are still under treatment. Two patients were admitted with bronchopleural fistula; one closed following adequate drainage and the other after a Schede thoracoplasty.

In group 3 are cases with pure tuberculous empyema without associated pyogenic infection but with active pulmonary tuberculosis. The object of treatment is twofold: To stop the formation of pus in the pleural cavity and usually to maintain collapse of the tuberculous lung. The simplest measure that may succeed is repeated aspiration of the pus with air-replacement, thereby maintaining collapse of the lung by pneumothorax. A phrenicectomy helps to maintain pulmonary collapse, especially if there is a tendency toward obliterative pleuritis. The great majority of cases that finally reach a surgical clinic, usually after an adequate trial of aspiration, can scarcely be expected to have the pleura rendered free of pus-formation by aspiration alone; closed or open drainage is strictly contraindicated because the empyema is a purely tuberculous one. In such cases extrapleural thoracoplasty is clearly the treatment of choice if there is no specific contraindication to it, and especially if it is desirable to produce permanent collapse of the diseased lung on the pneumothorax side; thoracoplasty usually results in the cessation of pus-formation in the pleura. If in such cases a needed thoracoplasty is contraindicated, phrenicectomy and continuing aspirations may palliate the symptoms. It is important that

tube-drainage should not be excluded from the patients of groups 1 and 3 because a single smear or culture of the aspirated pus fails to demonstrate pyogenic organisms; if a patient is highly toxic and does not respond properly to simple aspirations, repeated cultures should be made of the aspirated pus and these should be promptly incubated. In table 3 are reported the results in our 25 group-3 patients. They do not include the many cases of mild pure tuberculous empyema complicating pneumothorax therapy that we have seen in consultation, chiefly in sanatoria, and which disappeared after several aspirations, with air replacement.

TABLE 3

Group 3, 25 cases: pure tuberculous empyema with active pulmonary tuberculosis

LAST OPERATION	NUMBER OF CASES	CURED	IMPROVED	WORSE OR UNIMPROVED	DIED
Aspiration	3*				3
Phrenicectomy	1	1			
Extrapleural thoracoplasty†	21	16		1	4‡
Total	25	17		1	7
Per cent		68		4	28

* Hopeless bilateral pulmonary tuberculosis.

† All of the 21 patients had a preliminary phrenicectomy.

‡ One direct operative death, cardiac decompensation, 24 hours. Three deaths that may have been indirectly due to operation: (1) Bilateral tuberculous pneumonia and uraemia, 15 days; (2) abscess of thoracic wall and purulent myocarditis, 15 days; (3) tuberculous meningitis, 1 month.

Practically all of the group-3 patients who were referred to us had failed to respond to such simple therapeutic measures.

In group 4 are those patients with mixed tuberculous and pyogenic empyema, with associated active pulmonary tuberculosis. The objects of treatment are to evacuate the pus and sterilize the empyema cavity and usually to maintain collapse of the diseased lung. As in the cases of group 2, repeated aspiration even with antiseptic irrigations or instillations only exceptionally kills the pyogenic organisms. Closed or open drainage should, therefore, be instituted early when a brief trial of aspiration fails to do more than slightly and temporarily to improve the patient. As in group 3, phrenicectomy should usually be used early to relax the diseased lung and to lessen the size of the empyema cavity. Prolonged adequate drainage of an empyema cavity results in a tendency toward

complete or partial expansion of the lung. Only exceptionally in the cases of this group is this desirable, but, on the other hand, permanent collapse may be even less desirable if there are considerable dyspnoea and progressive pulmonary tuberculosis in the contralateral lung. For those cases in which permanent collapse is desirable, and particularly for those in which prolonged drainage has resulted in improvement in general condition but in only partial obliteration of the empyema cavity, a thoracoplasty is highly desirable. An extrapleural thoracoplasty with formalinization of the periosteum will either obliterate the empyema cavity or reduce its size, depending upon its prethoracoplasty size and

TABLE 4

Group 4, 30 cases: tuberculous and pyogenic empyema with pulmonary tuberculosis

LAST OPERATION	NUMBER OF CASES	CURED	IMPROVED	WORSE OR UNIMPROVED	DIED
Aspiration	2				2
Open or closed drainage	16	2	3	2	9
Extrapleural or/and Schede thoracoplasty	12	8	1		3
Total	30	10	4*	2	14
Per cent		33.3*	13.3*	6.7	46.7

Preliminary phrenicectomy was performed in 16 of the 30 cases. All of the thoracoplasty patients had had drainage.

*Since this article was written six months ago, two (one open-drainage and one thoracoplasty case) of the four "improved" patients are cured and the other two, having had extrapleural and Schede thoracoplasties within six months, have persistently negative sputum and their sinuses will soon be healed. Therefore, at the present time, 40 per cent of this group are cured and 6.7 per cent are improved.

the rigidity of its walls. If, after several months, a residual cavity should remain, it may be closed by a less extensive Schede thoracoplasty than would have been necessary, had an extrapleural thoracoplasty not been first used.

The results in our 30 group-4 cases are given in table 4. The patients classified as "cured" have completely obliterated empyema cavities, solidly healed wounds without a sinus, and the sputum, if any remains, is negative for tubercle bacilli. By "improved" we mean that the sputum is negative for tubercle bacilli but the empyema is still open and treatment is not completed. The unimproved patients in this group of our series have had only drainage, with or without phrenicectomy,

and in them thoracoplasty is contraindicated because of progressive bilateral pulmonary tuberculosis with cavitation. Fifteen of the 30 patients in this group had a bronchopleural fistula. Five of them are cured following thoracoplasty; one is unimproved and nine are dead. Three of those who died had had a spontaneous pneumothorax in the presence of hopeless bilateral pulmonary tuberculosis before admission to the hospital.

An analysis of the deaths in group 4 is interesting. The two patients whose empyemata were only aspirated were in such poor condition with far-advanced bilateral pulmonary tuberculosis at the time of admission that additional surgical measures were excluded; one died eight days and one two months after admission. The two patients who had only closed drainage were also desperately ill at the time of admission and both died six days later. Of the 7 patients who had only open drainage, four had virtually hopeless bilateral pulmonary tuberculosis, and died four days, seven days, fourteen weeks and several months, respectively, after admission; another patient died twelve days after drainage of the empyema from a perforated appendix and peritonitis; one died one month after admission from diphtheritic myocarditis, and one five weeks after admission from streptococcus bacteraemia and diabetic coma. Of the 3 patients who had a thoracoplasty and died, one died two hours after operation from myocardial degeneration and circulatory decompensation, one died fifteen days after operation from bilateral pneumonia and uraemia, and one died one year after operation from nontuberculous pneumonia, the patient having been cured of her tuberculous empyema and pulmonary tuberculosis. It may be seen in table 4 that the mortality rate was greatest when only aspiration was used, that it was less when closed or open drainage was used in the last operation, and that it was least in the thoracoplasty group. In spite of the facts this certainly does not mean that thoracoplasty is a safer operation than drainage or aspiration. The explanation is that those patients who were able to have thoracoplasty had survived what may have been a desperately ill state during which only aspiration or drainage could reasonably have been undertaken.

COMMENT

It is of interest to note in table 1 the difference in mortality between groups 2 and 4, in both of which the empyemata were mixed pyogenic and tuberculous. The group-2 cases, having no demonstrable active

pulmonary tuberculosis, had a low mortality, whereas the group-4 cases, most of which had active bilateral pulmonary tuberculosis, had a relatively high mortality. It is also interesting that the mortality in group 4 was practically twice that in group 3, the former having mixed pyogenic and tuberculous empyema and the latter pure tuberculous empyema, but both groups having active pulmonary tuberculosis.

The rather widespread prejudice that exists against the surgical management of tuberculous empyema is, we believe, chiefly based upon fear of a high surgical mortality. In this regard we feel that it is significant that only two of the 23 deaths that occurred in our 70 cases were directly and only 4 were perhaps indirectly connected with the surgical operation (table 1), and that 6 deaths occurred in patients who had had no other direct treatment than aspiration, and that 14 deaths were due to the continuing progression of the tuberculosis, principally in the contralateral lung. Thoracoplasty was used in 43 of the total of 70 patients. Of the forty-three, 32, or 74.4 per cent, are cured; 3, or 7 per cent, are improved; one, or 2.3 per cent, is unimproved; and 7, or 16.3 per cent, are dead.

We believe that attainment of good results in tuberculous empyema depends chiefly upon recognition of the importance of distinguishing between the four absolutely distinct types of the disease and upon a high degree of individualization in the application of the therapeutic measures that may be properly applied in each type. Reliance upon nothing but prolonged aspirations, with or without antiseptic irrigations or instillations, and without regard to the type of empyema being treated, inevitably results in a shockingly high mortality. An important cause of failure in those cases in which tube-drainage has been used is that frequently the tube is not placed at the most dependent part (with reference to a recumbent patient whose shoulders are slightly raised by pillows) of the empyema cavity, and that the tube is either too long, too short or too narrow, and particularly that the tube is removed before the cavity has become completely obliterated. Another cause of failure is that many of the thoracoplasties that are being performed for empyema are not planned to give maximal assurance of complete obliteration of the cavity and they are performed in so few stages as to make the operative mortality frightfully high.

TUBERCLE BACILLI AND MONILIA[1]

STEPHEN J. MAHER[2]

In spite of the fact that many interesting contributions in the last few years have been devoted to man's efforts to understand the yeasts called *monilia*, the yeasts called *monilia* are not yet understood. Where do they come from? What effect do they have on human beings? What is the significance of their occurrence in symbiosis with recognized germs of proved pathogenic power?

As everybody knows, these monilia are found frequently in tuberculous sputum. Incidental to some other work not yet ready for publication, I have, during the past twenty months, studied the monilia of tuberculous sputum, and have reached several rather startling conclusions which I think you will find interesting, even though you find them hard to believe.

If, to a specimen of carefully gathered tuberculous sputum which contains no monilia, there be added an equal amount or more of sterilized milk, it will be found a few days after the milk has curdled (preferably at room temperature) that the nuclei of the pus cells show a marked tendency to bud, and that many of the tubercle bacilli have been ingested by the pus cells, and that perhaps even now there have developed in the milk-sputum beautiful small nests of monilia, apparently related to the budding nuclei of the pus cell. Occasional individual monilia will be more or less acid-fast. If, however, there be found at this time that there are no monilia in the jar of milk-sputum, and that many of the pus nuclei are yet intact or nearly intact, a second portion of milk should be added to the milk-sputum. Almost invariably, after the caseation of this second portion of milk, monilia will make their appearance in the contents of the jars. This phenomenon will occur in nearly 100 per cent of the cases of tuberculous sputum examined and tested. There will be no development of monilia in the tuberculous sputum if sterile broth or

[1] An address, September 13, 1932, at the joint annual meeting of the North German Tuberculosis Society and the German Tuberculosis Research Association, Hamburg, Germany, under the Presidency of Professor L. Brauer.

[2] Connecticut State Tuberculosis Commission.

glycerine-broth or normal salt solution, or any other sterile solution of which I have knowledge be substituted for the milk. And, strange as it may seem, the monilia will develop in the sputum, no matter whether the milk is ordinary mixed milk from untested cows or the milk of cows tested and found free of tuberculosis, or commercially pasteurized milk, or carefully sterilized milk, or milk freshly excreted from the cows, or unheated milk that is old enough to have begun to thicken into an acid curd. The monilia will appear in the tuberculous sputum if the milk-sputum be placed in the incubator, but, in my experience, success is achieved more regularly if the mixtures are kept at room temperature. Of course, as soon as I learned that the monilia could be made to appear by using sterile milk, I used in these experiments only sterile litmus milk.

It seems evident therefore that in my experiments it is the presence of milk that was necessary for the development of buds on the pus nuclei and for the development of the monilia from the budding pus nuclei. On the other hand, Dr. P. Janvrin Marett of the Island of Jersey, who has written much on monilia, reports that he has been able to get monilia from 100 per cent of his cases of pulmonary tuberculosis. He however makes no attempt to study the origin of his monilia.

In discussing the origin of these monilia he includes in his report for 1929 the following significant paragraph:

> Some maintain that Monilias are harmless yeasts, struggling for existence in unhappy circumstances. Many agree that when no other organism in particular is present, Monilia infection may be diagnosed, but as soon as T.B. accompanies Monilia, the latter becomes a mere contamination, yet we know that Diphtheria may be a serious complication of Scarlet Fever and Typhoid of Malaria and that the recognition of these is the key to treatment. The presence of Monilias in pleural effusions, as the sole organism present, raises the question as to whence the so called contamination.

In my experience, monilia are present in less than 10 per cent of specimens of fresh tuberculous sputum, but, by the technique already described, they can be made to appear, at first few in number, but later in such numbers as to dominate the bacterial flora of the sputum and often to cause the disappearance from the sputum of all tubercle bacilli. These monilia that I have developed in tuberculous sputum are usually ovoidal or pear-shaped, but sometimes round. In one case, that of a man with severe tuberculosis of five years' standing, a large cavity in the upper lobe of the right lung, and with sputum loaded with tubercle

bacilli and almost no other bacteria, I tried in vain once a week for nearly a year to develop monilia from his sputum. On September first to my great delight I succeeded, but the resulting monilia were of different shape from any that I had previously seen. They were finger-shaped, and usually several times as long as usual and much more granular in appearance. Some of these granules were occasionally acid-fast, and very infrequently the whole organism would be more or less acid-fast. This same tendency to acid-fastness is shown by the ordinary smaller pear-shaped or round monilia developed from tuberculous sputum, but I have not found it in monilia from nontuberculous sputum. In my opinion, the longer, finger-shaped monilia from the cavity in this case were due to the impregnation of pus nuclei with whole tubercle bacilli. In support of this belief, I have found repeatedly that when the smaller ordinary monilia are planted with certain fast-growing paratubercle bacilli, and where the bacilli after a few days disappear from the culture, a good proportion of the ordinary small monilia have taken on the longer finger shapes.

Like the tubercle bacillus itself, the monilia from tuberculous sputum are gram positive, and cultures, when pure, are invariably neutral: they do not change litmus milk, despite the fact that they grow well in that medium.

Once the monilia have been discovered, they can be isolated and made to grow pure in subculture by ordinary laboratory procedures. The procedure that I prefer is to plant some of the sputum-milk on plain potato. Within 48 hours, the dry white growth, characteristic of yeast, will be seen on the upper sixth or third of the potato slant. From this white area, pure subcultures can usually be made on various media. At first it is advisable to plant the dry white of the potato on glycerinized media. When the type of the monilia has been fixed by several subcultures on glycerinized media, one may safely subculture on unglycerinized media. If, at any time, the culture should become contaminated by the development of cocci or diplococci among the monilia it can be easily purified by again planting on plain potato, preferably a week or two old.

Of course, I do not consider that the presence of tubercle bacilli in the sputum is necessary for the development of monilia or yeast of any kind in a given specimen of sputum-milk. These monilia occur or can be developed in the sputum of asthmatics or of cases of pulmonary cancer or of Hodgkin's disease, and in many other kinds of sputum that contain

diplococci or streptococci. In fact, in tuberculous sputum, it is usually not the whole tubercle bacillus that appears to activate the pus nucleus into budding. The granular or beaded tubercle bacillus appears to impregnate the pus nucleus with only a granule or polar bead, before the development of the bud on the nucleus begins.

And in the asthmatic cases it is the impregnation of the pus nucleus with a terminal element of the streptococcal chain that fertilizes the pus nucleus. We all know of the frequent occurrence of these monilia in pneumonic pus and in the pus from certain cases of empyema. Also, I have frequently been able to develop these monilia from the sputum of recently arrested cases of pulmonary tuberculosis, in which there were now no tubercle bacilli, but, instead, dozens of diplococci to every field.

The appended bibliography shows some of the disease conditions in which monilia have been found by recent writers.

Perhaps it seems a violent strain on your credulity to ask you to believe that a live vegetable element, like a coccus or diplococcus or the polar bead of a tubercle bacillus, or even the entire tubercle bacillus, when ingested by an animal cell, instead of destroying the animal cell or of being destroyed by such animal cell, may and often does cause this animal cell to give birth to vegetable cells, the monilia. If the strain on your credulity is so great that it breaks at this point, it is useless for me to proceed further, but, in the hope that you are still open-minded, I should like to add a few words.

In cultures that have been allowed to age, the monilia become more and more granular and often disintegrate into empty yeast shells surrounded by masses of granules, coccoids, cocci, diplococci, short rods made up at first of two diplococci end-to-end, and eventually into non-acid-fast and more or less acid-fast bacilli of good shape. I have here some cultures of acid-fast rods developed from old cultures that were originally pure cultures of monilia. The non-acid-fast forms have no pathogenic power when injected into guinea pigs, but some of the acid-fast forms develop abscesses at the point of injection and retain their acid-resistance when recovered and subcultured, but so far I have not been able with them to cause tuberculosis in guinea pigs.

I have had my attention drawn to a certain isolated European district, where it was said the inhabitants have no pulmonary tuberculosis, and where the food of the inhabitants consists chiefly of cheese, made from the milk of cows of which a large proportion are tuberculous.

Curious to learn something about the bacterial flora of this wonderful

cheese, I obtained a large portion of it, studied it under the microscope, subjected it to the same technique that I had used with tuberculous sputum and repeatedly had the same results; that is, I have isolated from this cheese monilia indistinguishable in characteristics from the monilia grown from the sputum-milk mixtures.

The answers to some of the questions probably in the minds of my hearers are: All the monilia that I have recovered from tuberculous sputum or from cheese made of milk from tuberculous cattle, are non-pathogenic to guinea pigs; but they do not cure or prevent tuberculosis in guinea pigs. When planted in liquid cultures of tubercle bacilli, these monilia at first outgrow and ingest the tubercle bacilli, but often, after a month or more in the incubator, the tubercle bacilli grow luxuriantly, stop the growth of the monilia and win the fight. If to scraped cultures of pathogenic tubercle bacilli on glycerine-agar slants, some glycerine-broth be added, and this be planted with monilia and the slants be kept at room temperature, there will appear on the slants and in the glycerine-broth pure cultures of a short non-acid-fast rod, that will crackle in the flame, but will not cause, cure, or prevent tuberculosis in guinea pigs. My monilia grow well either at 37°C. or at room temperature. Therefore, the experiment of planting them in cultures of certain paratubercle bacilli that grow only at room temperature, and then placing the cultures at 37°C., resulted as would be expected. The phagocytosis of the bacilli by the monilia was prompt and complete.

I refrain at this time from drawing any conclusions from the findings. I am unable to give the sequence of events that result in the appearance of monilia in the milk cultures of the cheese. The predominant bacteria in the first cultures from this cheese are gram-positive cocci, diplococci, and *Bacillus mycoidos 2nd*, a bearer of small usually acid-fast spores. Some of those other organisms may have a more important bearing on my problem than I have ascribed to them; but, to me, the strikingly dramatic and important finding was that of the monilia, apparently the same type as that that grew in the tuberculous sputum subjected to the same technique. From old cultures of these cheese monilia, in which the monilia have exploded, leaving in the test-tubes, beside some empty yeast cells, only faint coccal and bacillary shapes, I have grown pure cultures of partially or entirely acid-fast organisms that make very good pseudotubercle bacilli. On various facets of this problem, I am still working. Perhaps it would have been better if I had made no report until I had completely solved the problem. However, the subject

seems to me so important that I am anxious that the men and women of the great laboratories of the world should have an opportunity to visualize my somewhat bizarre dream, even though they, and not I, should be the first to see my dream realized.

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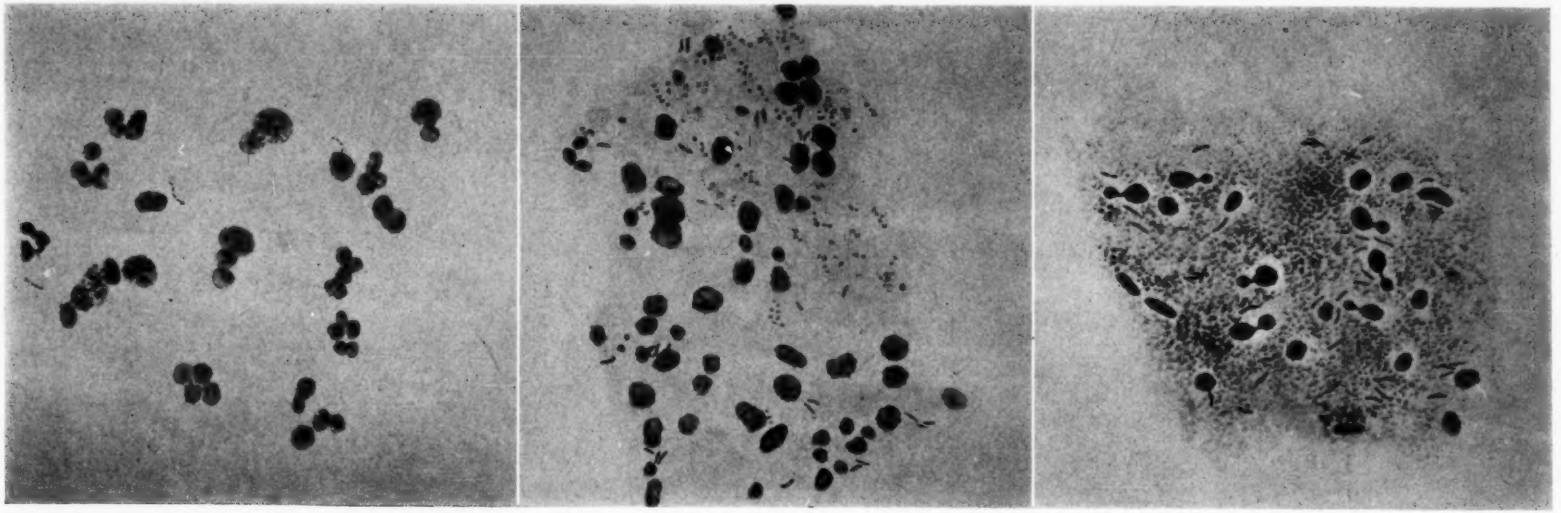

FIG. 1 FIG. 2 FIG. 3

FIG. 1. Buds of nuclei of pus cells simulating monilia, but no perfect monilia.
FIG. 2. First appearance of perfect monilia. Many budding nuclei.
FIG. 3. Perfect budding monilia appearing after 24 hours on potato.

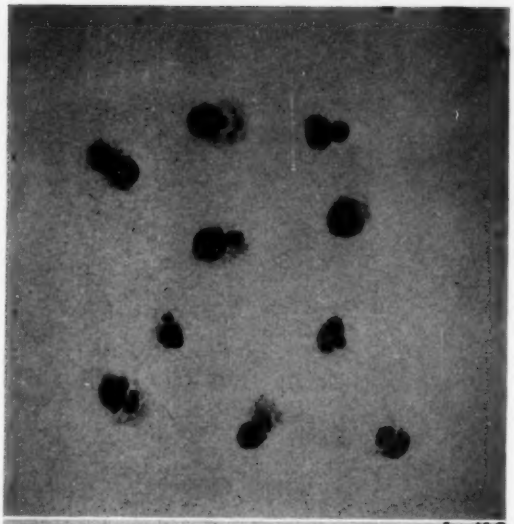

FIG. 4

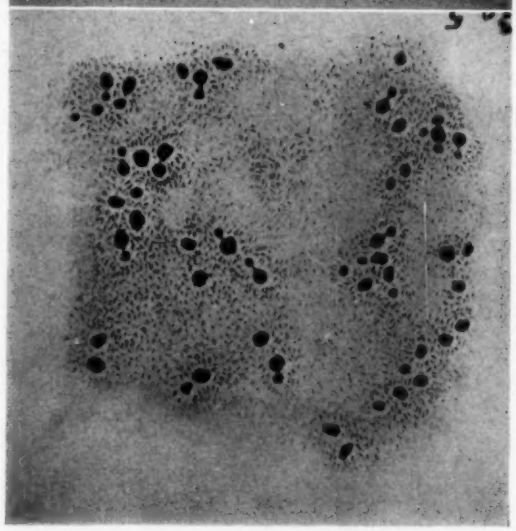

FIG. 5

FIG. 4. Budding pus nuclei appearing in tuberculous pleural serous fluid 48 hours after aspiration.

FIG. 5. Same serous pleural fluid as figure 4, after 48 hours on glycerine-agar at room temperature.

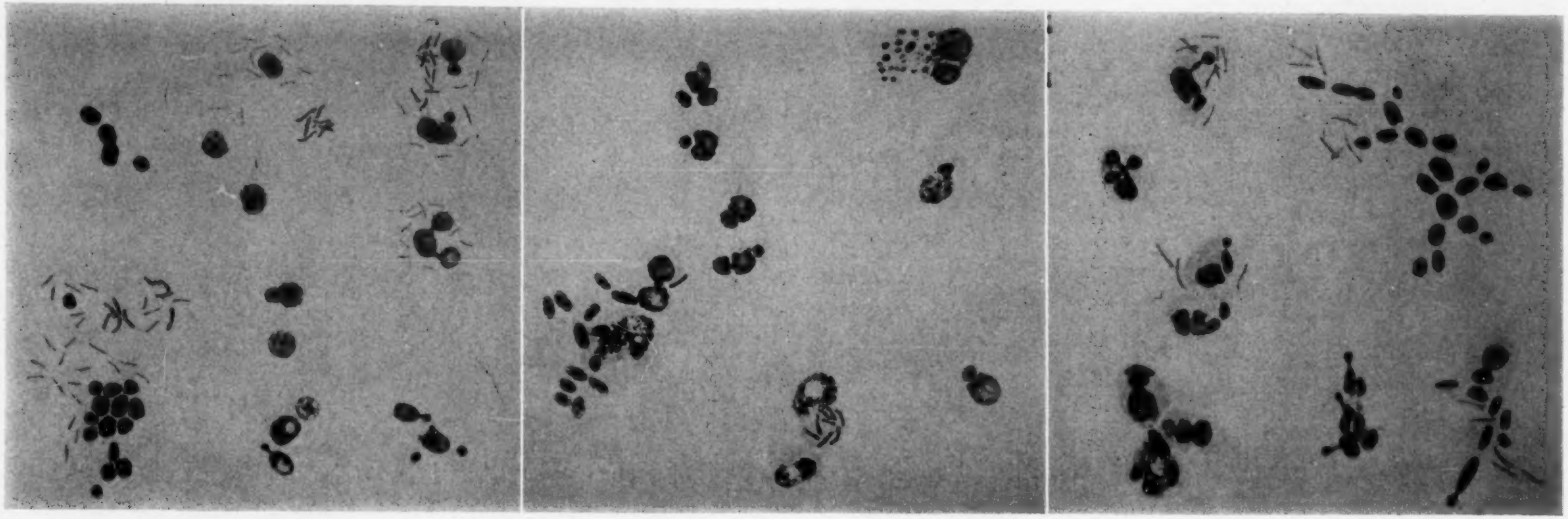

FIG. 6 FIG. 7 FIG. 8

FIG. 6. Sputum in which after one addition of milk there were no monilia. The smear was made a week after a second portion of milk was added.
FIG. 7. Another sputum in which a second adding of milk was required to bring about the development of monilia from the nuclei of the pus cells.
FIG. 8. A sputum in which the monilia appeared after the first adding of milk.

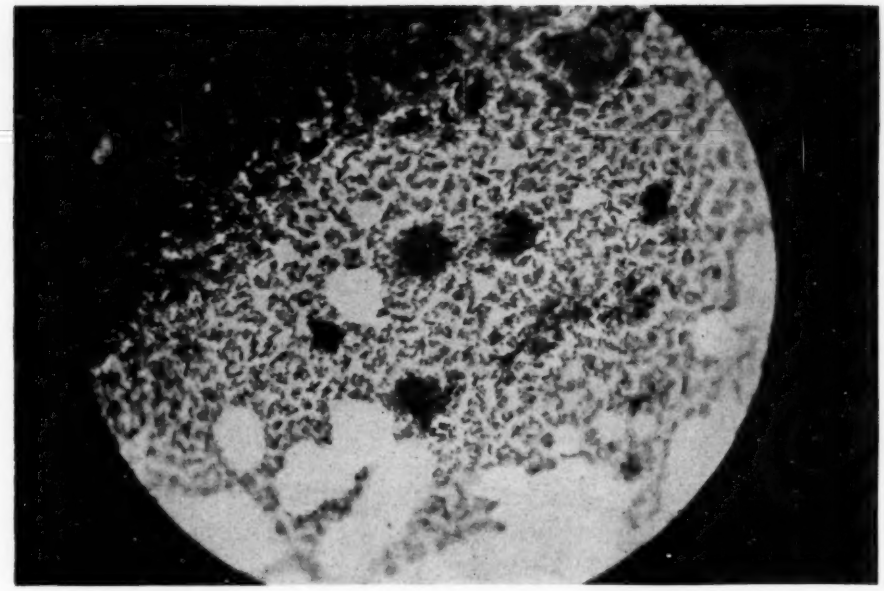

FIG. 9. Showing the end-result of monilia disintegration. The entire culture is practically pure granular bacilli and cocci. Only a few monilia cells remaining.

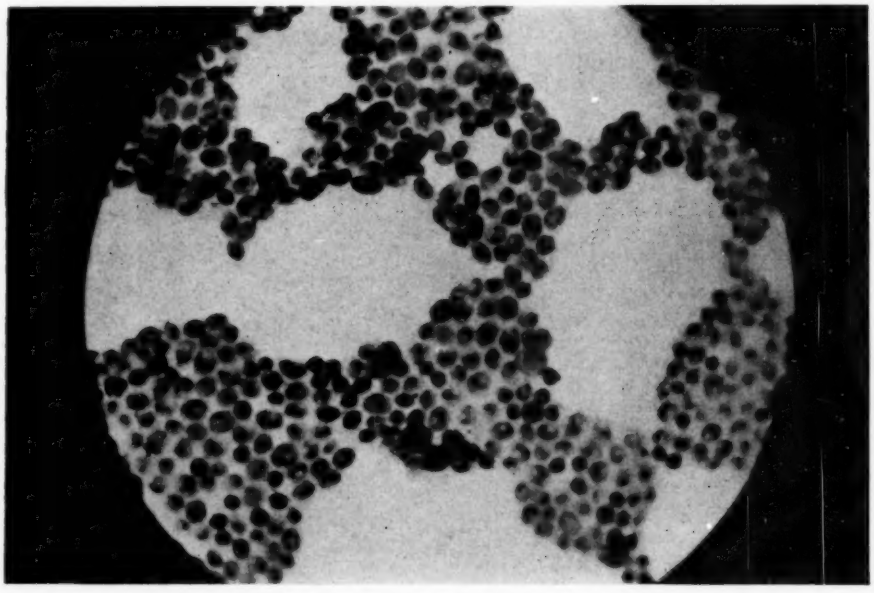

FIG. 10. Monilia from the sputum of a case suffering from cancer of the lungs

THE RELATION OF THE DUCTLESS GLANDS TO THE INCIDENCE AND DEVELOPMENT OF TUBERCULOSIS[1]

H. LISSER

INTRODUCTION

Fifteen years of predominant concern with clinical endocrinology derived from the diversified experience of medical teaching wards and clinics and private practice, taken together with the normal contacts of an internist with so ubiquitous a disease as tuberculosis, leads to an initial pronouncement: *Tuberculosis and diseases of the ductless glands are not commonly encountered together.*

It must be admitted, despite the gratifying advances in the prophylaxis and therapy of tuberculosis with consequent significant reduction of its incidence and mortality, that it still remains a familiar and formidable morbid entity. One may concede likewise that promising progress has been made in the recognition and treatment of endocrine disturbances and it is altogether likely that the total incidence of incretory derangements must exceed even that of tuberculosis. Therefore when two such prevalent medical conditions as tuberculosis and endocrinopathy companionate with relative infrequency, one is tempted to conclude that when they do occur together such a happening is to be interpreted as purely coincidental.

However, further reflection and investigation would term such a deduction as partly correct only; else there would be little purpose to this paper. It is perhaps this uncommon relationship which accounts for a rather sparse literature in this field, on the false assumption that infrequent occurrences excite small interest; whereas it is more nearly true that the *unusual* demands explanation. There are a fair number of scattered references to the incidence or relationship of tuberculosis to such endocrine maladies as exophthalmic goitre, Addison's disease, and diabetes mellitus. Very few efforts have been made to gather, sift, correlate and evaluate the reciprocal relationships which underlie the development or nondevelopment of tuberculosis in patients exhibiting

[1] Read by invitation at the annual meeting of the California Tuberculosis Association, Coronado, California, March 11, 1933.

ductless glandular abnormalities. This constitutes a noteworthy contrast to the numerous essays linking up disturbances of the endocrine glands with mental and psychic peculiarities, or with diseases in such special domains as the teeth, eye, ear, nose and throat, or gastrointestinal system.

May I not, therefore, before launching into the body of this paper, express my appreciation of the invitation to address this annual meeting of The California Tuberculosis Association? The subject was not of my choosing, but I am grateful for the urge which has helped to clarify my thoughts and compare them with others', and I hope with the result that what follows, though admittedly of no immediate importance, may not be wholly devoid of interest.

The subject can be approached from two directions: To what extent does tuberculosis invade endocrine structures and disturb their function? Or, the other way about,—to what extent do primary endocrinopathies contribute to the incidence or alter the course of tuberculosis? Both of these aspects will be considered and finally a word added as to whether therapy involving the ductless glands possesses any merit in the treatment of tuberculosis.

ENDOCRINE TUBERCULOSIS

Under this heading the ductless glands may be divided into two groups, depending upon their susceptibility to invasion by the tubercle bacillus. The adrenals, ovaries, testes and thymus (it still remains a question as to whether the latter structure is a true endocrine organ) are occasionally the seat of tuberculous infection; whereas the thyroid, parathyroid, hypophysis and pancreas seem to possess a remarkable antagonism toward the tubercle bacillus. Tuberculosis, whether primary or secondary, is found in this second group only with the greatest rarity.

The Thymus: Let us dispose of the thymus first:

In 1888 Jacobi (1) examined about 100 thymi of tuberculous patients. In his judgment tuberculosis of the thymus is not uncommon. He found it three times out of 60 cases in patients having died from diseases other than tuberculosis, and in one-fourth of all the cases in which tuberculosis was the cause of death. In all positive cases he was able to demonstrate the presence of tubercle bacilli in the thymus.

On the other hand, primary tuberculosis of the thymus is very rare. The majority of cases reported are doubtful, because enough care has not

been taken to ascertain if the original focus actually occurred in the thymus or whether the tracheobronchial lymph nodes, or the lungs were first involved. According to Crotti (2), about the only case of undoubted primary tuberculosis of the thymus is the one reported by Demine, that of a child whose parents were nontuberculous, and who died in the third month of general marasmus. Autopsy showed an enlarged thymus containing several tuberculous foci; no other evidence of tuberculosis could be found anywhere else in the body.

The tuberculous process may be miliary or caseous; the more common variety being of the secondary type in connection with caseous tuberculosis of the mediastinal lymph nodes. Often, however, in very advanced caseation of the mediastinal lymph nodes, one is rather surprised to find the thymus absolutely untouched.

Tuberculous abscesses in the thymus have been recorded by Carpenter (3) and Tixier and Feldzer (4).

The Adrenals: The most common and most important chronic infectious disease of the adrenals is tuberculosis.

It occurs in three forms: the miliary, the nodular and the diffuse fibrocaseous. The latter is most common, and is the usual anatomical finding in Addison's disease. In a study of 561 autopsy reports in Addison's disease, Lewin (5) found tuberculosis of the suprarenals present in 75 per cent of the cases and some authorities believe the incidence to be even greater.

In about 20 per cent of cases the tuberculosis is primary in the adrenals. Thus Elsässer (6) found general chronic tuberculosis in 133 instances, pulmonary tuberculosis in 235, other scattered foci of chronic tuberculosis in 85, and in 96 cases the adrenals alone were involved. In Elsässer's 530 cases there was bilateral adrenal involvement in 472, or 89 per cent. In Addison's original series of 11 cases, 5 showed caseous tubercles of both suprarenals.

It is thought, in tuberculous subjects, that the suprarenals may become infected from the neighboring mesenteric lymph nodes, or from the vertebrae, since some cases have been associated with caries of the spine.

The tuberculous process affects both the cortex and medulla of the gland in varying degree, with more or less caseation, or with softening, fibrosis or calcification. Tubercle bacilli have been found frequently in these foci. Macroscopically the glands may be greatly diminished in size, or, in some instances, so much enlarged as to present the appear-

ance of a tumor. The gland parenchyma shows varying degrees of destruction, the medulla and cortex as a rule being uniformly involved, but in some instances either the cortex or the medulla may be predominantly affected.

The frequency of tuberculous changes in thymico-lymphatic individuals has been ascribed by some writers (Wiesel, Hedinger, Goldzieher (7)) to a constitutional weakness consequent to hypoplastic pheochrome tissue.

The Testes: Hugh Young (8) finds tuberculosis that begins in the testes extremely rare and considers most reported cases open to some doubt; he has never observed one. Practically, it is always secondary to tuberculosis of the epididymis. In Young's series of genital tuberculosis the testis was involved in 8.3 per cent only, and many of these were late cases. The statistics have an important practical bearing, since the conclusion is obvious that, when operations in this region become necessary, testicles should always be spared if not positively involved. These organs are so necessary for the welfare of the patient from an endocrine standpoint that they should be preserved if possible. Incidentally, this applies with almost equal force to the ovaries, and in latter years surgeons and gynaecologists have come to recognize this, fortunately, and are less callous in their attitude toward removal of these vitalizing incretory structures.

Since tuberculosis usually involves the epididymis first its spread to the testicle, therefore, is commonly by way of the tubules. Miliary tuberculosis is of course an exception to this rule. The microscopic picture is the familiar one of tuberculosis: the testicle is enlarged and nodulated; there may be caseation, with fistula and even fungous formation; or healing with fibrosis and calcification. Davis (9) states that all testicular elements are equally involved; the affected testicle shows aspermatogenesis, but, if a portion is not involved, the interstitital cells retain their function until they are suppressed by fibrosis. Tubercle bacilli have been found in the apparently healthy testicles of tuberculous patients, according to Davis.

Fishberg (10) calls attention to a curious phenomenon, namely, that patients with tuberculosis in the male generative organs are more apt to succumb to tuberculous meningitis than those with tuberculous lesions in other organs,—33 per cent as against about 5 per cent.

The Female Generative Organs: Primary tuberculosis of the female generative organs is very rare, though in fatal pulmonary phthisis specific tuberculous changes are frequently found in the female pelvic organs; some authors, like Schlimpert and Krönig, have found this to be true in over 80 per cent of fatal cases of pulmonary tuberculosis. On the other hand, Fishberg (10), in 182 necropsies on tuberculous women at the Montefiore Hospital found only 8 with tuberculosis of the fallopian tubes, and one each of the uterus, ovary and vagina. The relationship of male and female gonadal tuberculosis to pulmonary tuberculosis will be elaborated upon later in this paper. This latter phase of the subject is of considerable interest and significance.

Having considered the first group of ductless glands which occasionally succumb to invasion by Koch's bacillus, we may turn our attention to the second group of incretory organs which seem to possess a formidable immunity to tuberculous infection, namely, thyroid, parathyroid, hypophysis and pancreas.

The Thyroid: Tuberculosis of the thyroid is rare. Rokitansky (11), in 1861, denied its existence, and Virchow (12) voiced the opinion that no organ in the body is so little predisposed to tuberculosis as the thyroid; and that such infection is of the utmost rarity and usually the result of tuberculosis of the neighboring structures which ultimately invades the gland by contiguity. Marine goes so far as to say "there is no recorded instance of *primary* tuberculosis of the thyroid." Gloyne (13) in 260 autopsies on tuberculous individuals found only one naked-eye tuberculosis of the thyroid. Similarly, in the highly susceptible guinea pig, experimentally injected with the tubercle bacillus, tuberculous lesions of the thyroid are apparently not common. However, thyroid-gland substance of various animals seems to have no bactericidal effect on the tubercle bacillus *in vitro* nor does the administration of thyroid substance to experimentally infected guinea pigs and rabbits, over a course of several weeks, arrest the disease. In other words, there appears to be little evidence for supposing that the thyroid itself has any direct antitoxic action in tuberculosis, and Gloyne deems it more likely that some anatomical reason accounts for the thyroid so frequently escaping infection. He adds that both heart and voluntary muscle may be cited as similar examples of this relative immunity and in all 3 cases a histological explanation is conceivable.

It is true that cases have been reported in which the thyroid showed tuberculous changes either at necropsy or after surgical removal. Mosiman (14) collected a number of these; but, at all events, they are rare. Fishberg (10) states that when the thyroid, derived from tuberculous cases, is examined histologically the changes are those of sclerosis as a rule, the direct antithesis of those found in Graves' disease. Róna (15) points out that, although the thyroid is occasionally involved in miliary tuberculosis, it has been repeatedly noted that the tubercle shows no tendency to further development, but, on the contrary, soon becomes encapsulated, often before reaching macroscopic size. A caseous thyroid gland is extremely infrequent.

The Parathyroids: Occasionally the parathyroids may be in the site of a tuberculous infection in association with a general miliary dissemination (Klotz (16)). Verebely, in a study of the lesions in 138 cases, found 2 involved in tuberculosis. Similar cases are also described by Benjamins, Eggers, Winternitz and others. Barker (17) mentions the interesting occurrence of the tetany syndrome in the course of a tuberculous meningitis associated with general miliary tuberculosis. In one such case, at autopsy, Winternitz (18) found miliary tubercles in a parathyroid gland.

The Hypophysis: Most authors consider tuberculous infection of the hypophysis as almost unheard of, but Simonds (19) seems to find it occasionally in generalized miliary tuberculosis, the lesion appearing either as a conglomerate tubercle, or as one or more miliary tubercles. He was able to collect records of 28 such cases. He believes that tuberculosis of the hypophysis should be classified as metastatic, resulting from an extension to the hypophysis from adjacent structures. When this happens the process is usually a carious one of the bones of the base of the skull, especially the body of the sphenoid bone, as in the cases of Sommer and Heidekamp; seven out of the 10 cases in Simmonds's series were characterized by miliary tuberculosis of the hypophysis associated with a tuberculous meningitis. The 3 cases of Beck, Zenoni and Cushing are mentioned in which the tuberculosis of the hypophysis was regarded as primary; at any rate, it was specifically stated that no tuberculosis was found elsewhere in the body. The infection, when it does occur, is rarely of sufficient severity to interfere with the normal functions of the pituitary body, but it is conceivable that tuberculosis of the hypophysis could be the cause of that peculiar clinical syndrome, first described by Simmonds, namely, "hypophyseal cachexia."

Atkinson (20) has recently published a remarkable monograph on acromegaly in which he sets forth in a systematic manner details of all cases ever published in any language up to the end of 1930, numbering 1,319. In 20 of these 1,319 cases pulmonary tuberculosis was a complication and death was due to it in six.

I have copied the following data from Atkinson's book for those who might be interested:

Pulmonary tuberculosis has been seen in the following cases: Barr, Bourneville and Regnault (2), Brissard and Meige, Cushing, Eltsteter and Schroeder, Ferrand and State, Hutchinson, W., Labbe, and Langlois, Landrieux and Wahl, Launnois and Roy, Loewenberg, Poncet and Lériche, Moutier, Poindecker, Robinson, Rotky (glands also), Schultze and Fischer, Shaw (probably), Squance-Murray (20 cases) and death resulted of it in 6 of the above certain cases (Bourneville and Regnault (2), Eltsteter and Schroeder, Hutchinson, Poindecker, Schultze and Fischer).

Sugar was associated with tuberculosis in 4 cases (Barr, Ferrand and State, Launnois and Roy, Squance-Murray). The tuberculin reaction has been found positive (Barrett, A. M. Kinnicott), and in Lombrosos's case, acromegaly was stated to have started after an haemoptysis. In one case only was the hypophysis reported caseous, like TB (Fortun y André).

The Pancreas: Róna (15) states that the pancreas is practically immune to tuberculosis. It is also interesting that if pancreas substance is added to the culture-medium the growth of the tubercle bacilli is inhibited. Chabral ascribes this antagonistic influence to the rich lipase content of the pancreas.

TO WHAT EXTENT DO ENDOCRINE DISEASES AFFECT THE INCIDENCE AND ALTER THE COURSE OF TUBERCULOSIS?

Although for the sake of thoroughness consideration has been given to the incidence and extent of tuberculous invasion of endocrine structures by the tubercle bacillus, the degree to which tuberculosis itself is modified or transformed by alterations in endocrine function constitutes a theme of far greater import.

Hyperthyroidism: Disturbances of thyroid function are among the most common of all endocrine disorders, and the clinical manifestations of excessive thyroid secretion are probably more frequently encountered, or at any rate recognized, than the syndromes of hypothroidism. Hyper-

thyroidism (exophthalmic goitre, Graves' disease, Basedow's disease, toxic adenoma, in other words, thyrotoxicosis) comprises a familiar clinical entity. Indeed, especially in its milder forms, commonly met with in young persons, it is frequently mistaken for phthisis. I agree with Fishberg (10) that patients with tachycardia, liability to sweat at the least exertion or excitement, languor, dermographism, loss of weight and even a slightly elevated and unstable temperature are not to be considered tuberculous unless a physical examination of the chest and roentgenography reveal a distinct pulmonary lesion; nor can we resort to basal-metabolism estimations to decide the diagnosis, as they may be confusing and have to be disregarded in favor of clinical evidence. An elevated rate has been found (McBrayer) in 59 per cent of 54 tuberculous patients and in 61 per cent of 23 incipient cases. If the diagnosis remains in doubt Musser advises treating the patient as tuberculous until proved otherwise. There is less danger from handling a case of hyperthyroidism as if it were tuberculous, than from treating a tuberculous patient as if he were thyrotoxic.

Perhaps the even more confusing syndrome of neurocirculatory asthenia (otherwise known as effort syndrome, irritable heart, or autonomic imbalance) is still more readily mistaken for incipent tuberculosis.

Goetsch (21), ten years ago, strongly recommended his "epinephrin test" as of the greatest value in the differential diagnosis in many conditions simulating hyperthyroidism, of which incipient tuberculosis is probably the most important. He contended, fortunately for the differentiation, that tuberculosis uncomplicated with hyperthyroidism uniformly gives a negative reaction to the test, and stated that this fact had afforded means for distinguishing early tuberculosis from hyperthyroidism, two conditions which clinically simulate each other so closely that mistakes in diagnosis are frequently made. Many writers have agreed that this differential diagnosis is by no means an easy task. Jennings points out that certain cases of mild toxaemia with cough and chronic pyrexia bear such a close resemblance to incipient pulmonary tuberculosis that a differential diagnosis may require a very close analysis of all the clinical and laboratory findings. Symptoms common to both are fatigability, tachycardia, pyrexia, cough and dyspnoea, and derangement of digestion and metabolism.

It is interesting to inquire into the incidence of goitre among tuberculous individuals. von Massur (22) records that, 1904–1916, 3,222 patients were treated in the *Neuen Heilanstalt für Lungenkranken* at Schömberg. Among these, there were 150 with more or less large or definitely

visible and palpable goitres (4.7 per cent) and 8 characteristic cases of Basedow's disease. Turban-Davos reports a goitre incidence among tuberculous patients of 13 per cent. Percentages reported naturally vary with the examiner and what he considers a goitre; furthermore, endemic goitre regions should be expected to yield a higher incidence.

Statistically, at least, the presence of goitre would seem to have a favorable influence on the tuberculosis. For instance, 71 per cent of the goitre-tuberculous group represented "closed" cases of tuberculosis, as compared to 44 per cent of the non-goitre-tuberculous group. Also, only 15 per cent of the goitre group remained "open" with bacilli in their sputum, whereas 40 per cent of the non-goitre group remained "open." Furthermore, 45 per cent of the goitre-tuberculous group were permanently fever-free, as against 35 per cent of those without goitre. The number of days required for cure of tuberculosis averaged definitely lower in the tuberculous-goitre group, namely 116 days, as against 135. What was considered a cure was obtained in 65 per cent of the tuberculous-goitre group as against 46 per cent in the non-goitre-tuberculous group. From the above statistics it would seem reasonable to assume that the presence of goitre in a tuberculous patient provides a favorable prognosis as far as the tuberculosis is concerned. As long ago as 1827 Cassan reported a family, part of the members having tuberculosis, while the others, free from tuberculosis, were goitrous.

Joll (23) in his recent book, *Diseases of the Thyroid*, states that experience has shown that there is very little tendency for thyrotoxic patients to develop tuberculosis either of the lungs or elsewhere and, contrariwise, those who are already suffering from tuberculosis rarely develop thyrotoxicosis. Virchow went so far as to contend that a definite antagonism existed between goitre and tuberculosis, and that the existence of the former was tantamount to proof of the absence of the latter.

Fishberg (10) interprets hyperthyroidism symptoms in patients with incipient tuberculosis as indicative of a favorable prognosis, and affirms it as his opinion that, within certain limits, hyperactivity of the thyroid is incompatible with progressive pthisis.

The authors cited represented but a tiny fraction of the great host of writers who have commented with almost universal agreement on the prominent rôle which the thyroid gland plays as an immunizing or prophylactic agent against tuberculosis.

What would seem to constitute supporting evidence for such an assumption is the relative susceptibility to tuberculosis of *hypothyroid* indi-

viduals. Rolleston in a personal communication to Joll stated that myxoedema and tuberculosis are often associated. The observation has been made that hypothyroidism is probably nine times as frequent as hyperthyroidism in the average run of cases of chronic pulmonary tuberculosis.

Charrin (24) found that insufficiency of the thyroid gland lowered the resistance of the body to the tubercle bacillus, and this same observation has been corroborated by Mackenzie (25) in the majority of myxoedematous patients and also by Bandelier and Rœpke (26).

Diabetes Mellitus: Another very common endocrine disease, namely that due to a deficiency of the internally-secreting portion of the pancreas, is diabetes mellitus. Joslin (27), who has compiled some of the most valuable statistics in an exceptionally large experience with diabetes, states that "tuberculosis was formerly responsible for about one half of the deaths of diabetic patients, but that today, in private practice, it seldom occurs." Montgomery (28), in 1912, made a critcal summary of the literature pertaining to this matter, and concluded that tuberculosis is not more frequent among diabetics than among the rest of the population of the same age, to which Joslin agrees. On the other hand, Banyai (29) (1931), cited by Fishberg, compiled statistics from the more recent American literature of 8,520 cases with diabetes and found the incidence of tuberculosis about 2.6 per cent, which indicates that tuberculosis occurs about three times more frequently in diabetics than in the general population of this country. Pulmonary tuberculosis has been diagnosed but once in any diabetic child seen by Joslin; in no instance has a death from this cause been reported subsequently, and he recalls no instance in American medical literature. Joslin found the percentage of deaths among diabetics (in his own series) due to tuberculosis, as compared to the total number of diabetic deaths, to be 4.8 per cent (in 1928), which was close to the percentage of tuberculous deaths to the total number of deaths in Massachussetts, namely 5.6 per cent. Of his 103 fatal cases of tuberculous diabetics the average duration of the diabetes was 5½ years, which is a fairly long duration. Furthermore, only 8.7 per cent died in coma, which was considerably below the coma percentage in the whole group of diabetics; and he thought that this might be explained by the emaciation and lack of food-intake in the tuberculous patients which perhaps lessened the severity of the diabetes.

Diabetes rarely occurs in a tuberculous patient; when the two diseases are found together, the diabetes has almost invariably preceded the

tuberculosis, and the latter makes its appearance very insidiously. The prognosis of diabetes complicated by tuberculosis was bad and is still serious. There seems to be disagreement as to whether the use of insulin has improved the prognosis as far as the tuberculosis is concerned. Extraordinary to relate, however, diabetes, even of the severest grade, may disappear when the tuberculosis reaches an advanced stage. For instance, Joslin (27) mentions the case of a patient aged 51 years, who after nine years of diabetes, with a total loss of 30 pounds and tolerance for 84 gm. of carbohydrate, developed active bilateral pulmonary tuberculosis with positive sputum. In the course of a year he gained 20 pounds, became sputum-free, and raised his tolerance for carbohydrates 100 gm., and, in so doing, used but 24 units of insulin daily. Another case is cited in which tuberculosis developed in an extremely severe type of diabetes of 8 years' duration; an extreme grade of acidosis completely disappeared and a minus carbohydrate balance of 40 gm. was converted into a positive one of 60 gm. Joslin is of the opinion that the fasting and loss of weight would improve the tolerance of even the severest diabetic, and adds that the treatment of diabetes complicated by tuberculosis is the same as for diabetes alone, and that the use of insulin has not altered this dictum. In other words, he contends that the diabetes should be treated first as the primary disease and that the initial undernutrition is so helpful to the diabetes that it can soon be disregarded and the patient fed a liberal amount of food for his tuberculosis. He regards insulin as a helpful aid in permitting a generous diet and does not believe that it is of any harm to the tuberculosis.

Fishberg (10), viewing the situation from the tuberculosis standpoint, reacts somewhat differently. He has observed diabetic patients with quiescent lung lesions, who had been doing well for years, enter sanatoria to become sugar-free, which they promptly attained on starvation, but developed exudative lung lesions which rapidly progressed to a fatal issue. Naunyn, Williamson, and Magnus-Levy have commented on the greater frequency of pulmonary haemorrhage in tuberculous patients who have diabetes, and Fishberg found such haemorrhage as a cause of death three times as frequent among diabetic tuberculous patients than among the nondiabetic tuberculous patients. He considers insulin a dangerous therapeutic agent in tuberculous diabetics.

Statistics may sometimes be misleading. It is at least a somewhat surprising observation that Fishberg (10), in a practice with thousands of tuberculous patients, derived from a class peculiarly liable to diabetes,

namely Jews, found very few tuberculous patients who were observed to develop glycosuria while suffering from active tuberculosis. In connection with this, it is pertinent to recall the words of Joslin (30) who states, "It does seem strange that in the large group of resting tuberculous patients who are overfed, diabetes should be so uncommon, in view of the fact that lack of exercise and overnutrition are two prime factors in its development."

Parathyroid Dysfunction: Important and indeed spectacular advances have been made in recent years with respect to our knowledge of the functions of the parathyroid glandules. We have been familiar for a long time with the fact that certain forms of tetany, more particularly that variety consequent to inadvertent removal of the parathyroids in the course of goitre operations, were due to inadequate parathyroid secretion. We were also aware of the fact that the administration of calcium would to some degree supplement for this deficiency, but it has only been somewhat over five years ago that a parathyroid hormone was identified by Professor Collip and the final proof brought forward that this extract plays a prominent rôle in mobilizing calcium. It is the lack of this secretion in certain forms of tetany which is responsible for the symptoms of this syndrome, which, furthermore, is invariably associated with a definitely low blood-serum calcium. On the basis of this fundamental physiological and chemical discovery, it was possible for the first time to conceive of a clinical disorder due to excessive parathyroid secretion which, because of constant withdrawal of calcium from the skeletal storehouse, resulted in abnormally high concentration of calcium in the blood-serum and, over a period of months and years, in cysts and rarefactions of the bones—the hyperparathyroid disease—*osteitis fibrosa cystica*, known for many years as *von Recklinghausen's disease*, the cause of which heretofore had been shrouded in mystery.

Both these endocrinopathies, *hypoparathyroid tetany*, and *hyperparathyroid osteitis fibrosa cystica*, are relatively uncommon. Therefore, unless there are clinical disturbances related to parathyroid dysfunction with which we are not as yet acquainted, it would seem unlikely that these ductless glands play any conspicuous rôle in influencing either the incidence or the course of tuberculosis. Mention might be made however of the observation that patients with tetaniaparathyreopriva seem to be more susceptible to tuberculosis (Róna (15) and Kaufmann (31)). Ordinarily, these patients are likewise hypothyroidic and their greater suscep-

tibility to tuberculosis may be due to this latter complication rather than to their parathyroid deficiency. One is also tempted to speculate on whether a state of hypocalcaemia might not prove to be somewhat of a hindrance to the calcified healing processes of tuberculosis.

Adrenal Deficiency: Adrenal deficiency, as exemplified in Addison's disease, is another rather rare endocrinopathy. There has been much theorizing over possible milder forms of adrenal inadequacy, but no convincing proof of such clinical states has been as yet forthcoming. Some of the symptoms noted commonly in pulmonary tuberculosis have been ascribed to a possible dysfunction of the adrenals, among these being low blood-pressure, pigmentation of the skin, as well as the weakness and lack of endurance.

In view of the fact that in nearly 90 per cent of cases of Addison's disease tuberculous changes are found in the adrenals, it is distinctly noteworthy that active tuberculosis of the lungs is very rare among them; and when lung lesions are found at necropsy they are ordinarily of the sclerotic type. In fact, many authors have observed that the tuberculous lesions in the lungs found in cases of Addison's disease are almost invariably of slight extent and healed. This rather startling phenomenon is sufficiently arresting to warrant reflection. It would seem justifiable to advance the hypothesis that a state of suprarenal insufficiency, even though brought about by tuberculosis, actually protects the individual against tuberculosis.

Prior to the discovery of the adrenal cortical hormone (independently by Swingle and Pfiffner, and Hartman) all subjects of Addison's disease inevitably died, usually within three years; and it should be emphasized in this connection, that their death was not due to tuberculosis, either of of the adrenals or elsewhere. These patients succumbed because their bodies no longer contained sufficient adrenal cortex to maintain life. In other words, they died of their endocrine deficiency and not of the tuberculosis which caused the endocrine deficiency.

By this time the listener or the reader, as the case may be, may have received the impression that the author, as an "endocrine specialist," has been attaching an undue importance to this field of clinical medicine. Lest such a thought arise, it might be appropriate to point out that such a reaction might repercuss in the form of a boomerang. Fortunately for

me, one of your own distinguished authorities, Maurice Fishberg (10), emphasizes that

> reciprocal relations between pulmonary tuberculosis and physiological and various pathological processes are of immense importance to those who have tuberculous patients under their care. They have great bearings on the original diagnosis, prognosis, and treatment of the tuberculous disease. A knowledge of these interrelations is especially needed by those whose practice is limited to institutions devoted exclusively to the treatment of tuberculosis, where physicians are liable to become "tuberculosis specialists," oblivious of the fact that their patients are humans—and capable of suffering from diseases other than that caused by the tubercle bacillus and that an intercurrent disease may have an influence, at times a very favorable one, more frequently the reverse, on the tuberculous process.

Hypophyseal Dysfunction: Despite the fact that the hypophysis is just now occupying the centre of the stage in ductless-gland research, and has been, figuratively, enshrined with such epithets as "Motor of the Gonads" and "Master Gland," its influence, if any, on the incidence or development of tuberculosis remains to be investigated. That its functional status should have some bearing in this regard, even though indirectly, seems nevertheless quite conceivable. One need but recall its specific and perhaps major responsibility for skeletal growth, and its profound importance in the achieving of and continuance of sexual maturity.

Surely all of you who have had occasion to observe tuberculous children over a period of years have noted that many of them are undersized until they reach 12–14 years of age, when they may rather rapidly become even taller than the average for their "race stock" (Fishberg (10)). Many of these tall youths exhibit signs of dyspituitarism, such as prognathism, long extremities and large wrists and fingers. I agree with Fishberg that it has not yet been established as to whether these changes can be ascribed to tuberculous alterations of the pituitary or to toxic effects on its function. On the whole, tuberculosis retards growth when attacking children under 12 years of age and seems to stimulate it during the adolescent years.

No doubt you have also observed that the secondary sexual characters in young tuberculous subjects are apt to be delayed in their appearance and that stigmata of infantilism are rather common among them. Tuberculous adolescent girls are liable to menstruate scantily and even complete amenorrhoea for many months is not uncommon. Whether this

happening is attributable to lack of the anterior pituitary sex hormone, or to ovarian deficiency, may be disregarded for the moment. Further consideration of sexual disturbances will be postponed to the paragraphs dealing with gonadal dysfunction.

Even in the absence of any outspoken hypophyseal endocrinopathy, the factor of constitutional type and inherited characteristics, producing either a fairly dominant or relatively weak pituitary gland, must play a part in the patient's capacity to cope with a tuberculous infection.

Gonadal Dysfunction: Many curious and even surprising observations have accumulated pertaining to the reciprocal relations between phthisis and the functional status of the gonads. Let us inquire first into the information obtained from experimental investigations.

Bricker (32) found that guinea pigs, experimentally infected with tuberculosis, lost weight fairly rapidly, but that castrated animals maintained their weight for a long time despite the tuberculous infection. Stated statistically, Zibordi (33) found that control animals survived 75 to 79 days after infection with tuberculosis; castrated males 83 days and castrated females 230 to 270 days. Apparently the physical-chemical metabolism is so altered by castration that the animal seems to have obtained a certain protection against the tubercle bacillus. Curatullo and Farulli, and also Loewy and Richter, etc., were able to show that oxidation processes are diminished in castrated animals. An increase in calcium has been produced by castration, and it is reasonable to suppose that such an increase may be helpful in healing tuberculosis. The cholesterol level is raised in castrates and lymphocytosis is produced also, factors which have been considered beneficial to tuberculous patients. The above excerpts constitute but a fragment of the numerous experimental investigations, the great majority of which are harmonious with the concept that gonadal deficiency has a favorable protective influence on the course of tuberculosis.

Clinical experience with human beings yields a similar conclusion. In most cases of tuberculosis of the female generative organs the lungs have been found free from active disease. Bauer (34) and Róna (15) also have observed males who developed hypogenitalismus, in whom the pulmonary tuberculosis became markedly ameliorated and pursued a mild chronic course over a great many years. Many cases of tuberculosis in women over 40 years of age show the effects of hypofunction of the gonadal organs more than they show those of the tuberculous toxaemia and

Fishberg (10) calls attention to the fact that fibroid phthisis is most common in persons over 40 years of age and that tuberculosis in the aged pursues, as a rule, a very sluggish course, all of which is suggestive in this connection.

It may not be inappropriate at this point to refer to the relative rarity of tuberculosis in truly obese individuals and that in such exceptional instances the consumptives survive for a very long time. Obesity as a rule develops following the artificial or natural menopause and almost invariably is characteristic of castrated animals.

One cannot lightly brush aside the endocrine significance which attaches to the incontestible fact that the years between infancy and puberty constitute, as Krause (35) phrases it,

> Mankind's "golden age"—as regards tuberculosis. . . . . First, the mortality falls sharply from that maintained in infancy; and soon reaches a nadir that is maintained until late childhood, when the rise to the mortality peak of manhood begins. Never before and never again afterward do we find such low tuberculous death-rates as obtain in childhood; and this too is the period when opportunities for infection are most common and infections are being received most frequently. If it were a period of peculiar freedom from disease and respiratory disorders and ill-health in general we might grasp at the circumstances to explain the paradox of declining mortality with mounting infection. But childhood is not such a period; it is the very reverse, and is, withal, that time of life when any consciousness as to personal cleanliness and bodily care is at its lowest and when these needs are least looked after.

What a contrast faces us immediately after puberty and from then on during the years of highest sexual virility. It is precisely during this epoch, when the function of the gonad is at its greatest, that the tuberculous process is so often exceedingly acute and progressive. This is a particularly dangerous age for tuberculous patients.

Moreover, the accumulated observations of tuberculosis specialists the world over, for the most part agree on the increased sexual irritability and even excessive venery displayed by tuberculous patients of this age-period. W. H. Peters (36) goes so far as to say that "every physician has been impressed by the almost disgusting and sometimes revolting persistence of the sexual instinct in consumptives, even late in the disease." Fishberg (10) adds

> It is remarkable that in the advanced stages of the disease, when the body is extremely emaciated, the muscles atrophied and the vital forces apparently at

their lowest, sexual potency may be retained. Even shortly before death a consumptive may impregnate his wife, and a woman who has lost one half of her normal weight and is subject to frequent hemorrhages, runs a febrile temperature, sweats and coughs distressingly, is, at times, seen in a pregnant state.

Indeed, three directors of sanatoria—Kohler, Krause, and Marquard,—in answer to queries from Weygandt (37), sent the interesting information that the patients in their sanatoria had accused the doctors of secretly putting aphrodisiac drugs into the milk, or other food. That this heightened sexual excitability seems peculiar to the tuberculous toxaemia appears to be borne out by the experience that in other chronic diseases in which patients are idle, eat well and may become despondent (taking their pleasures while they may), they do not indulge in sexual excesses to the same extent as the tuberculous.

Furthermore, the statistical investigations of Pearson (38) and also Kacprzak (39) disclose a heightened fertility over the normal nontuberculous stock of the same class in the community at large. Indeed: "the fertility of marriage is enhanced by tuberculosis of either one of the consorts," and "the mating of both parents tuberculous seems to show a higher fertility than the mating of both non-tuberculous."

For centuries many physicians reported the observation that pregnancy often ameliorated the disease in the female tuberculous patient and some, like Cullen, in the eighteenth century, actually recommended marriage for tuberculous girls for this reason. Fishberg (10) quotes Warren, who in a prize essay, published in 1857 said, "Pregnancy, coition, etc., are particularly desired by women affected with phthisis which constitutes a pointing of Nature toward a remedy for the evils by which the system has been invaded." Many authorities since that time have expressed somewhat similar views, modified to the extent however of noting that the tuberculous patient seems better during pregnancy: that "the disease appears in abeyance;" but they add that after the child is born the phthisis is apt to advance at a rapid rate. This at once suggests the idea that the temporary improvement during gestation is due to the absence of catamenial intoxication. It is of course generally known that the toxaemic manifestations of tuberculosis are almost uniformly aggravated at each menstrual period. Although the concept, that pregnancy is beneficial to the tuberculous woman, is undoubtedly an exaggeration, carefully evaluated statistical data do justify the statement that pregnancy has very little, if any, adverse influence on the course of tuberculous disease

which is quiescent, benign or healed. "Such patients pass through pregnancy unscathed as a rule." And though, no doubt, women suffering from active spreading exudative lesions will suffer an aggravation of the disease as a result of pregnancy, labor and lactation, it is nevertheless remarkable that "It is extremely rare that a tuberculous woman should die with the fetus in utero."

Summing up, it can be fairly stated, that one cannot afford to disregard the endocrine status of an individual when attempting to estimate his tuberculous prognosis. The penetrating influence of these extraordinary organs during the period of growth, the age of sexual awakening, the epoch of intense maturity, and the period of declining years is too vast and too vital to be without vibration in a disease such as tuberculosis.

And, to be more specific, the hyperactive thyroid, the relatively negative suprarenal, and the insufficiently functioning gonad, each, in its own peculiar way, seems to shield the individual against the onset or advance of tuberculosis.

THE RÔLE OF THE DUCTLESS GLANDS IN THE TREATMENT OF TUBERCULOSIS

If the above observations and ruminations possess any merit it may be reasonably asked whether endocrine extracts have any place in tuberculosis therapeutics. The answer to this in any case must be extremely cautious, and, for all present practical purposes, probably negative. Nevertheless a consideration of this subject would not be complete or adequate without a few remarks.

Because of the great rarity of tuberculosis in thyrotoxic individuals, and because of the enlargement of the thyroid in guinea pigs experimentally infected with tuberculosis (the latter, interpreted as a response to a demand for increased function), the thought has been ventured (Webb (40)) that it might be desirable to utilize thyroid extract in selected cases of human tuberculosis. On the whole, this would seem to be a dangerous doctrine to translate into practice. The writer, however, has not hesitated to administer thyroid substance, with great care and under strictest observation, in a few tuberculous patients, who were unnecessarily and uncomfortably obese. Such symptoms as dyspnoea may be somewhat relieved thereby, but, generally speaking, if the patient suffers from no symptoms which may be attributed to the obesity, they are best left alone as regards their corpulence. If actual hypothyroidism complicates tuberculosis, then thyroid supplementary therapy is not

only justified but positively indicated since the very state of thyroid deficiency is apt to aggravate tuberculosis.

The active parathyroid extract, parathormone, has been tried in combating haemoptysis on the theory that its mobilization of calcium will hasten coagulation. The author has had no personal experience with the use of this product for this purpose but the interested reader is referred to the article by Cantarow and Gordon (41).

The divergence of opinion with regard to the safety or danger of insulin in the treatment of tuberculous diabetics has already been referred to. A word at this point though is indicated regarding the aid to be derived from insulin in combating malnutrition. An insulin "fattening cure" is worthy of trial in tuberculous patients whose appetite is refractory.

The introduction of the new adrenal cortical hormone (*Eschatin, Cortin*) into clinical medicine has been so recent that we are not justified in recommending its use outside of Addison's disease as yet, but it is conceivable that this preparation may have some merit as a specific tonic. Of the many remarkable effects accomplished by this preparation, in patients with Addison's disease, the most constant is its production of increased strength, endurance and well-being. French clinicians have utilized adrenal organotherapy in tuberculosis patients, claiming excellent results; so much so, that Sergent (42) and others propose to treat every case of frank tuberculosis with adrenalin or adrenal extracts. They have given 1 to 2 mgm. of adrenalin, or the corresponding amount of whole adrenal gland, daily in fractional doses over a series of 10 days; after a rest period of 10 days, the treatment was repeated. The writer only mentions this example of enthusiastic credulous organotherapy gone rampant, *in order to condemn it*, especially since oral adrenal therapy heretofore has been almost certainly utterly useless.

If states of gonadal hypofunction are really desirable in tuberculous patients, then the exhibition of ovarian or testicular extracts would seem to be positively contraindicated. Surely their use should be restricted to alleviating distressing menopausal symptoms in a patient who also happened to have tuberculosis.

Surely it would be a stout-hearted radical who would presume to urge castration as a therapeutic measure for combating tuberculosis. But at least it should be mentioned that castration was advised by Bumm (1908) for the treatment of pregnant tuberculous women, and Martin in 1913 reported good results in 60 cases. Kehrer (43) considered this procedure the best treatment available. Warnebros recorded that oper-

ative castration following abortion exercised a most favorable effect on pulmonary tuberculosis.

Finally, the conception has been advanced, that some of the benefit derived from the generally accepted means of treating tuberculosis, namely hygienic, dietetic, heliotherapeutic and climatic, has ensued through the intermediation of the ductless glands. This paper has reached such undue length that time and space forbid further elaboration of this intriguing idea, but for those to whom such a notion seems altogether fanciful the writer recommends perusal of the thoughtful thesis of Róna.

In conclusion: I am tempted to observe that some authors are temperamentally better fitted to write on subjects concerning which they entertain positive constructive convictions, based on original observations of their own; others are by nature more disposed to judicial reviews or critical appraisal of the work of others. It so happens that the topic of my discourse forces me into the latter rôle, to which I am not so readily habituated.

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EXTRAPLEURAL PARAFFIN PNEUMONOLYSIS FOR PHTHISIS[1]

R. B. McINDOE AND JOHN ALEXANDER

For years we were opposed to the use of extrapleural pneumonolysis with paraffin filling because it is contrary to accepted surgical practice to place a foreign-body permanently in the tissues. The fact that we were frequently seeing certain patients with cavernous phthisis for whom all other probably effective collapse-therapy procedures were contraindicated, the great majority of whom would probably die from tuberculosis if not aided by surgery, finally compelled us to adopt the operation in spite of its defects.

Although our series of 42 patients is a small one, and the longest period of postoperative observation is only two years, we are reporting the results and other pertinent data at this time because we do not know of any published series of cases in which sufficient statistical information is given to furnish an adequate basis for judgment as to the worth of the operation.

Our first operation was performed on October 18, 1930, and the last, that is included in this report, on September 30, 1932. The condition of every one of the 42 patients was known to us as late as August, 1932, and of some as late as November, 1932. A bilateral operation was performed in one case, and, as the important factors of extrapleural cleavage and cavity closure must be considered separately for each side, this patient will be counted as two cases in spite of the fact that the clinical result, "improved," will be erroneously reported twice. In four patients, paraffin was introduced both anteriorly and posteriorly on the same side at different operations. The paraffin was introduced only anteriorly in 19 patients and only posteriorly in eighteen. In summary, 47 operations were performed on 42 patients.

Pneumothorax was attempted in all but one patient who, having been in a sanatorium for several years, requested that a paraffin pneumonolysis be used in preference to pneumothorax. In only 4 patients was any

[1] From the Michigan State Sanatorium, Howell, Michigan, and the University of Michigan Hospital, Ann Arbor, Michigan.

pneumothorax whatever obtained; in them it was wholly unsatisfactory, and there was no indication for intrapleural pneumonolysis.

Either temporary or permanent phrenic-nerve interruption was performed in 24 of the 42 cases before the pneumonolysis operation was decided upon. In 18 cases the interval between the operations was more than seven months and in 6 cases from two to five months. The cavities became larger in 15 of the 24 patients following phrenic interruption, slightly smaller in two, and did not appreciably change in size in seven.

A preliminary phrenic operation was not performed in 18 cases, chiefly because the nature of the cavity made it appear unlikely that closure would result. Furthermore, most of these patients had bilateral active tuberculosis, eight having bilateral cavitation, and it was felt that a phrenic paralysis might later be needed for the contralateral lesions if the pneumonolysis were successful in closing the cavity. Actually, one permanent and two temporary phrenic interruptions were later performed on the contralateral side and 5 permanent interruptions on the homolateral side. Another reason for not inducing phrenic paralysis on the side of the intended pneumonolysis was that, in a number of the 18 cases, the lower half or two-thirds of this lung was sound and it seemed desirable to retain it for full function in view of considerable tuberculous involvement of the opposite lung.

In table 1 are reported the results of our 43 paraffin pneumonolyses with regard to clinical effect, cavity closure and presence or absence of tubercle bacilli in the sputum, and also our ability or inability to create at the time of operation a sufficiently large extrapleural space to make closure of the cavity probable. Before operation all of the patients had open cavities and tubercle bacilli in the sputum, and the majority had active bilateral tuberculosis. Our last report shows that 69.9 per cent were arrested, apparently arrested, quiescent or improved, and 30.1 per cent were unimproved or dead. Twenty, or 69 per cent, of the cavities for which a satisfactory extrapleural cleavage was obtained were closed.

At the time of operation we knew of no treatment other than pneumonolysis or thoracoplasty that could reasonably have been expected to close the cavities. We have divided the patients into three groups, according to the risk of thoracoplasty.

In group I are three patients whose lesions did not extend below the second or third rib anteriorly and whose cavities were small and in whom there was no active disease in the contralateral lung. In all of them the thoracoplasty risk would have been very small, but a pneumonolysis was

chosen instead because it offered even a smaller risk and because it seemed probable that it would close the cavity. At present, however, we feel that in the majority of such cases a limited thoracoplasty is the preferable operation, because it is more certain of closing a pulmonary

TABLE 1

Results§

	NUMBER OF PATIENTS	EXTRAPLEURAL CLEAVAGE		CAVITY		TUBERCLE BACILLI IN SPUTUM		APPARENTLY CURED†	ARRESTED†	APPARENTLY ARRESTED†	QUIESCENT†	IMPROVED†	UNIMPROVED†	DIED†
		Satisfactory	Unsatisfactory	Closed	Unclosed	−	+							
Group I*.....	3	2	1	2	1	2	1	0	2	0	0	1	0	0
Group II*.....	3	2	1	2	1	2	1	0	1	1	0	1	0	0
Group III*.....	37	25	12	17	20	14	23	0	3	5	5	11	7	6
Total.....	43	29	14	21	22	18	25	0	6	6	5	13	7	6
Per cent of total..	100	67.4	32.6	48.8	51.2	44.1	55.9	0	13.9	13.9	11.7	30.4	16.2	13.9

* Group I, good thoracoplasty risk. Group II, poor thoracoplasty risk. Group III, thoracoplasty definitely contraindicated.

† The criteria for the results that are given in this and the following tables are those of the National Tuberculosis Association. Our use of paraffin pneumonolysis is too recent to permit inclusion of any of our cases in the apparently cured group, which demands absence of all symptoms of tuberculous activity for two years or more. Only six months are required for the arrested group and three months for the apparently arrested group.

§ During the fourteen months that have passed since these tables were prepared, 19 additional patients have had extrapleural pneumonolysis with paraffin filling. In 18 of them extrapleural cleavage was satisfactory, in one unsatisfactory (not including 5 patients in whom cleavage was so unsatisfactory that no paraffin could be introduced). Among the 19 patients the cavities are closed and tubercle bacilli are absent from the sputum in 17; the cavities are open and tubercle bacilli are present in two. One of the patients who appear in the tables later had a posterior pneumonolysis supplementary to an unsuccessful anterior pneumonolysis and the cavity is closed and the sputum negative. Our final figures for the cases in which some paraffin could be introduced (except one in which no paraffin was introduced and which was erroneously included in the tables) are: total number of patients, 62; satisfactory extrapleural cleavage 75.8 per cent, unsatisfactory 24.2 per cent (70.1 per cent and 29.9 per cent, respectively, if the 5 cases in which no paraffin was introduced are included); cavity closed 62.9 per cent, unclosed 37.1 per cent; tubercle bacilli absent 58.1 per cent, present 41.9 per cent.

cavity and because its success is not dependent upon a satisfactory extrapleural cleavage and it is less subject to such a delayed complication as discharge of the paraffin. In two of the 3 patients the extrapleural cleavage was satisfactory, the cavities closed, and the sputum is negative for tubercle bacilli and the disease arrested fifteen and eleven months,

respectively, after operation. In one patient the cleavage was unsatisfactory, the cavity did not close, and four months after operation a thoracoplasty was performed, which closed the cavity and now, twelve months after the thoracoplasty, the disease is arrested.

In group II are 3 patients who had a cavity surrounded with rather dense infiltration extending no lower than the second or third rib, but who had a small amount of tuberculous infiltration in the opposite lung which was known to have been active within one month of the pneumonolysis operation. On account of the lesions in the opposite lung we considered thoracoplasty to present a greater than average risk and for this reason chose pneumonolysis. In 2 cases there was improvement and in one case no apparent change in the lesions in the opposite lung. In the 2 cases in which extrapleural cleavage was satisfactory, the cavities closed, and in one patient the disease is arrested and in the other apparently arrested, each twenty-five months after operation. In the third patient, the cleavage was unsatisfactory but improvement followed; seventeen months after operation a thoracoplasty was performed, which closed the cavity and resulted in arrest of the tuberculosis fourteen months later. Before operation on group-II patients we now decide whether or not we consider them justifiable risks for an immediate thoracoplasty should it be found at operation that extrapleural cleavage is unsatisfactory.

Group III (table 2) is composed of 37 patients who were such poor thoracoplasty risks that this operation was clearly contraindicated. In them pneumonolysis offered the only reasonable hope of cavity closure. It is the favorable results of 64.9 per cent in this otherwise desperate group that has convinced us that paraffin pneumonolysis is virtually an indispensable operation for certain cases of phthisis.

In the 37 patients of group III the strict contraindication to thoracoplasty was more or less extensive active tuberculosis in the contralateral lung in 32 cases; in addition, two of these patients had renal tuberculosis, one emphysema and one syphilis. The contraindications in 5 other patients were old age and poor general condition in two, old air-embolic (pneumothorax) hemiplegia in one, myocardial degeneration in one and pernicious anaemia in one.

Twenty-nine of the 37 cases in group III had far-advanced and eight moderately advanced tuberculosis before pneumonolysis. At the time of pneumonolysis, which in the majority of the cases was after months of sanatorium observation, the prognosis was considered to be virtually

hopeless in 23 if no operation were performed. The prognosis in 11 other patients was considered poor, in that only after further prolonged bed-rest might they possibly have become suitable risks for thoracoplasty. In only 3 patients did we believe that there was a reasonably good chance that a thoracoplasty might become a safe operation after further prolonged bed-rest. In the entire group of 37 cases, extrapulmonary complications seemed to us permanently to contraindicate thoracoplasty in eight. Paraffin pneumonolysis rendered 11, or 37.9 per cent, of the remaining 29 cases suitable thoracoplasty risks; actually, thoracoplasty

TABLE 2

*Results in group III**

MONTHS AFTER OPERATION	NUMBER OF PATIENTS	APPARENTLY CURED	ARRESTED	APPARENTLY ARRESTED	QUIESCENT	IMPROVED	UNIMPROVED	DIED	EXTRA-PLEURAL CLEAVAGE		CAVITY		TUBERCLE BACILLI IN SPUTUM	
									Satisfactory	Unsatisfactory	Closed	Unclosed	−	+
½–1	2	0	0	0	0	0	0	2	1	1	1	1	0	2
2–6	8	0	0	2	0	4	2	0	7	1	6	2	5	3
6–12	11	0	2	2	2	1	3	1	9	2	6	5	6	5
12–18	7	0	1	0	2	0	1	3	3	4	3	4	2	5
18–24	9	0	0	1	1	6	1	0	5	4	1	8	1	8
Totals.....	37	0	3	5	5	11	7	6	25	12	17	20	14	23
Per cent of total..	100	0	8.1	13.6	13.6	29.6	18.9	16.2	67.6	32.4	45.9	54.1	37.8	62.2

* *Group III:* Patients presented such poor thoracoplasty risks that this operation was clearly contraindicated.

was then done in only two of them, the others not needing it. In no case was a paraffin pneumonolysis used secondary to a thoracoplasty.

Fifteen of the 37 patients had moderate or severe tuberculous laryngitis before the pneumonolysis operation; 16 had symptomatic evidence of tuberculous enteritis; 19 had symptoms of moderate or severe pulmonary tuberculous activity, and 18 of low-grade activity, seven being afebrile.

In 17 patients among the 37 in group III the cavity became closed following operation. Fourteen of these 17 had had bilateral phthisis and there was bilateral decrease of the infiltration in fourteen. In the remaining 3 cases there was bilateral increase of what had been very extensive lesions and two of these 3 patients are now dead. In 20 cases

the cavity was not closed. In eight of them there was unilateral or bilateral increase of the lesions, this apparently being directly due to the operation in four and not connected with the operation in four. In 12 patients there was no change in the area of tuberculous involvement, or there was a slight decrease.

With regard to the clinical results in group III, one of the patients whose disease is now arrested and who has gained 25 pounds in weight and is doing part-time work, had been critically ill before operation, and had severe tuberculous laryngitis and tuberculous colitis in addition to his cavernous pulmonary lesions. One of the apparently arrested patients has gained 50 pounds since operation. Three of the 5 quiescent patients have negative sputum and are in excellent condition; one of them had had severe haemoptyses shortly before operation. The 2 quiescent patients who still have tubercle bacilli have, respectively, only 2 and 5 cc. of sputum daily.

Of the 11 patients who are classified as improved, five have been operated on within from two to six months and six more than one year ago. All are afebrile. Four have been discharged from hospital or sanatorium. Two of the 11 patients have negative sputum. Seven cases are classified as unimproved. The prognosis without operation had been considered practically hopeless in six of the seven. At present one patient feels fairly well, but complains of fatigue and has cough and positive sputum; the tuberculosis in another has continued to progress and the outlook is hopeless; the operation was responsible for extension of the lesions in 3 patients (these same cases were mentioned in the paragraph before the last), the chance of ultimate improvement in one being favorable and in two poor. Three of the 7 patients who were unimproved by pneumonolysis have had thoracoplasties; in two of the three the cavities are closed and the sputum is negative now, seven and twelve months, respectively, after the thoracoplasty. The third patient's cavity was not closed by pneumonolysis and a partial thoracoplasty was performed thirteen months later to close a cavity in the contralateral lung, but unsuccessfully, and the patient died twenty-one months after the pneumonolysis operation. The results of thoracoplasty are reported only in table 6.

Six of the 37 patients in group III have died. Two of the deaths, which occurred five and twenty-five days, respectively, after operation, resulted from an operative tear of the lung while attempting to separate firm extrapleural adhesions. This complication occurred early in our

experience with the operation when we were not fully aware of the danger of using more than the very gentlest pressure in separating extrapleural adhesions. We believe that this accident will never again occur in our hands. Three patients died seven, sixteen and seventeen months, respectively, after pneumonolysis, from progression of bilateral tuberculous lesions; the operation had closed the cavity in one and failed to do so in two. The sixth death occurred in a patient whose clinical course from its beginning suggested that he was almost wholly lacking in essential resistance to tuberculosis. The cavity was almost completely closed by paraffin pneumonolysis, and then it enlarged, and eighteen months after the first operation a thoracoplasty was added, and for a time the cavity could not be seen, but later a cavity appeared and the tuberculosis spread to the opposite lung. For these lesions a wholly satisfactory pneumothorax was induced, but the disease advanced in spite of it and a pleural effusion developed with resulting intense dyspnoea and cyanosis. The patient died twenty-one months after the paraffin-pneumonolysis operation.

As extrapleural pneumonolysis is usually used only for patients whose cavernous lesions are localized to one part of a lung, and the success of the operation in closing pulmonary cavities is the best criterion of its value. The omission of bismuth from the paraffin mixture and the use of the Potter-Buckey diaphragm for postoperative roentgenograms give almost certain assurance that the outline of an open cavity may be seen after operation. Disappearance of tubercle bacilli from the sputum is, of course, of great importance, but their persistence does not necessarily indicate that the cavity has not been closed if there happen to be active tuberculous lesions in the opposite lung. All of our patients had positive sputum before operation and 44.1 per cent became negative after operation. Five of our 42 patients had blood-streaked sputum and nineteen had frank haemoptysis of 5 cc. or more before operation. Only 2 patients, both with unclosed cavities, had haemoptysis, four and seven months, respectively, after operation.

In table 3 is shown the effect of the operation upon all the cavities in our three-group series, according to their size and the condition of their walls (Max Pinner's classification) and, in table 4, according to their position. The thickness and rigidity of the moth-eaten and irregular-walled cavities tend to prevent complete closure of the cavities, even when the optimal amount of paraffin has been used.

It is an interesting fact that if a cavity is seen to be open in the first

postoperative roentgenogram, it is likely that it will remain open, in spite of the continuing influence of contracting fibrous tissue in the walls of the cavity. Twenty-one of the twenty-two that have remained open were seen to be open when the first postoperative roentgenogram was taken within a week or two after operation, and in one case it was ques-

TABLE 3

Fate of all cavities according to size and type

SIZE	NUMBER OF CAVITIES	MOTH-EATEN AREAS	CLOSED	UNCLOSED	ROUND OR OVAL CAVITY	CLOSED	UNCLOSED	HEAVY IRREGULAR CAVITY-WALL	CLOSED	UNCLOSED	TOTAL CLOSED		TOTAL UNCLOSED	
											Number	Per cent	Number	Per cent
cm.														
0–½	4	4	2	2	0	0	0	0	0	0	2	50	2	50
½–2	8	0	0	0	3	2	1	5	5	0	7	87.5	1	12.5
2–4	21	0	0	0	10	5	5	11	3	8	8	38	13	62
4–6	8	0	0	0	0	0	0	8	3	5	3	37.5	5	62.5
6–8	2	0	0	0	0	0	0	2	1	1	1	50	1	50
Totals	43	4	2	2	13	7	6	26	12	14	21		22	
Per cent of total		100	50	50		53.8	46.2		46.2	53.8	48.8		51.2	

TABLE 4

Position of all cavities

POSITION OF CAVITIES	NUMBER OF CAVITIES	CLOSED		UNCLOSED	
		Number	Per cent	Number	Per cent
Supraclavicular	16	10	62.5	7	37.5
Infraclavicular	26	11	42.3	15	57.7
Midlung	0	0	0	0	0
Basal	1	0	0	1*	100
Totals	43	21	48.8	22	51.2

* This cavity is probably closed. A known bronchiectasis remains.

tionably present. Eighteen of the 21 closed cavities could not be seen in the first postoperative roentgenogram and in 3 cases their presence was doubtful. Only 4 patients whose cavities became closed continued to have positive sputum for more than three months after operation.

It is apparent that the greater the operative collapse of the lung, the greater is the chance of closure of the pulmonary cavity. In an extrapleural-pneumonolysis operation, attainment of the optimal collapse is

dependent upon the absence of such firm extrapleural adhesions that they cannot be divided with safety. The term "satisfactory extrapleural cleavage" that appears in some of the tables means that we were able to obtain what we considered at the time of operation to be a sufficient separation of the parietal pleura from the thoracic wall to cause closure of the pulmonary cavity by virtue of the amount of paraffin that was introduced into the extrapleural space. We hesitate, on account of undue pressure upon the mediastinal organs, to introduce more than 500 cc. of paraffin at any one operation, and in some patients this much would not be safe.

In table 5 are given the results with regard to cavity closure, presence of tubercle bacilli in the sputum, and the clinical effect, according as the extrapleural cleavage was satisfactory or unsatisfactory and also as the anterior or posterior operative approach was used. The significance of these figures is that the results were very much better when the extrapleural cleavage was satisfactory than when it was not and that the posterior operative approach not only gave a greater proportion of satisfactory cleavages than the anterior approach, but the clinical results in the satisfactory cleavages with a posterior approach were superior to those in the satisfactory cleavages with an anterior approach. When we began to use paraffin pneumonolysis we were not aware that the anterior approach tended to give relatively inferior results and, because technically it is a somewhat easier operation than the posterior one, we used it in approximately the first half of our series. It is reasonable to assume that the results in our whole series are less good than they are likely to be in future series;[2] this is indicated in table 5, which shows that 68.4 per cent of the cavities were closed by the 19 posterior operations, whereas only 33.3 per cent were closed by the 24 anterior operations. Incidentally, in three of our anterior pneumonolysis patients we later added a posterior pneumonolysis, which completed closure of the cavity in one of them; the extrapleural cleavage was satisfactory in one of the remaining two, but the cavity did not close. We added an anterior to a posterior pneumonolysis in one patient and the cavity became closed.

The size and position of the cavity to be closed and the thickness and resistance of its walls, as well as the greatly varying sizes of the patient's chests, obviously are factors that determine the optimal amount of paraffin that is needed to close a cavity. In our 20 cases in which the

[2] See footnote of table 5 for results of 19 additional cases.

TABLE 5

*Results according to approach and extrapleural cleavage**

APPROACH		EXTRAPLEURAL CLEAVAGE				CAVITY				TUBERCLE BACILLI IN SPUTUM				STATUS OF PATIENT											
		Satisfactory		Unatisfactory		Closed		Unclosed		−		+		Apparently cured		Arrested		Apparently arrested		Quiescent		Improved		Unimproved		Died	
Anterior	Posterior	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
−	−	29	67.4	−	−	20	68.9	9	31.1	18	62.0	11	38.0	−	−	6	20.7	6	20.7	3	10.4	6	20.7	6	20.7	2	6.8
−	−	−	−	14	32.6	1	7.1	13	92.9	1	7.1	13	92.9	−	−	−	−	−	−	2	14.3	7	50.0	1	7.1	4	28.6
+	−	12	50.0	−	−	7	58.4	5	41.6	5	41.6	7	58.4	−	−	3	25.0	2	16.6	−	−	3	25.0	2	16.7	2	16.7
+	−	−	−	12	50.0	1	8.3	11	91.7	1	8.3	11	91.7	−	−	−	−	−	−	1	8.3	5	41.6	2	16.6	4	33.5
−	+	17	89.5	−	−	13	76.5	4	23.5	12	70.6	5	29.4	−	−	3	17.6	4	23.6	3	17.6	3	17.6	4	23.6	−	−
−	+	−	−	2	10.5	−	−	2	100.0	−	−	2	100.0	−	−	−	−	−	−	−	−	1	50.0	1	50.0	−	−

*All of the 19 additional patients reported upon in the third footnote of table 1 were operated on by the posterior route. Combining these cases with the posterior-route cases in this table, extrapleural cleavage was satisfactory in 92.1 per cent, unsatisfactory in 7.9 per cent (81.4 per cent and 18.6 per cent, respectively, if the 5 cases in which no paraffin was introduced are included); in the 35-patient satisfactory-cleavage group the cavity was closed in 85.5 per cent and tubercle bacilli are absent in 82.8 per cent; in the 3-patient unsatisfactory-cleavage group the cavity is unclosed in 100 per cent and tubercle bacilli are present in 100 per cent.

extrapleural cleavage was satisfactory and in which the cavities became closed, the amount of paraffin used varied between 24 and 712 cc. (an-

TABLE 6

Subsequent surgery on homolateral side for residual cavity and positive sputum

ORIGINAL PARAFFIN PNEUMONOLYSIS	PHRENIC PARALYSIS	SUPPLEMENTARY PARAFFIN PNEUMONOLYSIS	THORACOPLASTY	RESULTS AND REMARKS
Anterior 11– 8–30	7–23–31	Posterior 10–18–31	2–25–32	Also contralateral pneumothorax. Died 8–12–32.
Anterior 11–20–30	5–23–31	Posterior attempt unsuccessful 4–28–31	4–28–31	Cavity closed. Tubercle bacilli negative. Arrested.
Anterior 1– 8–31	5– 6–31			Cavity open. Tubercle bacilli positive. Posterior pneumonolysis to be attempted.
Anterior 4– 4–31		Posterior 11– 9–31		Also contralateral phrenic paralysis. Cavity open. Tubercle bacilli positive. Unimproved.
Anterior 9–19–31			1– 6–32	Cavity closed. Tubercle bacilli negative. Arrested.
Anterior 6–23–31			1–11–32	Cavity closed. Tubercle bacilli negative. Apparently arrested.
Anterior 11–25–31		Posterior 1– 4–32		Cavity closed. Tubercle bacilli negative. Full-time work; arrested.
Posterior 2– 4–32		Anterior 5–27–32		Cavity closed. Tubercle bacilli negative. Apparently arrested.
Posterior 1– 4–32	3–24–32			Contralateral 6-rib thoracoplasty, 4–5–32. Cavity closed. Tubercle bacilli negative. Quiescent.
Posterior 6–22–32			7– 8–32	Cavity closed. Tubercle bacilli negative. Quiescent.
10	4	5	5	

terior and posterior stages); seventeen of the 20 cases had between 150 and 400 cc. of paraffin. The two moth-eaten cavities that were closed had from 300 to 400 cc. of paraffin, the seven round or oval cavities had

from 70 to 350 cc., and nine of the 11 heavy irregular-walled cavities had from 150 to 300 cc., one had from 350 to 400 cc. and one had 712 cc. Nine of the closed cavities were from 0.5 to 2 cm. in diameter, eight were from 2 to 4 cm., and two were from 4 to 6 cm. One 6- to 8-cm. infraclavicular cavity was closed with 712 cc. of paraffin. One 4- to 6-cm. cavity had 200 to 250 cc. of paraffin, and one had 250 to 300 cc.

It is interesting to note that approximately the same amount of paraffin was used in the group considered in the preceding paragraph as for the 9 cases in which there was satisfactory extrapleural cleavage but in which the cavities did not become closed. Among these nine, one moth-eaten cavity was not closed with 250 to 300 cc. of paraffin nor was one with 350 to 400 cc. The only round or oval cavity in the group was not closed with 548 cc. The six unclosed heavy irregular-walled cavities had from 100 to 500 cc. of paraffin. One cavity, 0.5 to 2 cm. in diameter, was not closed by 250 to 300 cc. of paraffin, nor another by 350 to 400 cc. Two 2- to 4-cm. cavities were not closed by 300 to 350 cc. of paraffin.

In 14 cases extrapleural adhesions prevented the formation of a sufficiently large extrapleural space for the estimated optimal amount of paraffin. Thirteen of these cavities failed to close; in one case no paraffin was introduced, in one 24 cc., in three 50 to 100 cc., in three 100 to 150 cc., in two 150 to 200 cc., in three 200 to 250 cc. and in one, with a cavity of only 2 to 4 cm. in diameter, 250 to 300 cc. One of the 14 cavities had a diameter of 0.5 cm., eight of from 2 to 4 cm. and five of from 4 to 6 cm. One cavity of a diameter of 4.5 cm. closed wholly unexpectedly with a paraffin filling of 109 cc. The position of the extrapleural adhesions that prevented a satisfactory pulmonary collapse in the desired place was at the very apex of the lung in 5 cases, in the upper costovertebral gutter in 4 cases, in the posterior axillary region at the level of the second rib anteriorly in 2 cases, in the midaxillary line at the level of the second rib anteriorly in 2 cases, and anteriorly at the level of the clavicle in one case.

Mere relaxation of the walls of a cavity is not necessarily enough to close it, as the figures for both the unsatisfactory and satisfactory extrapleural cleavage cases show. A further demonstration of this fact is available in the measurements of the shift of position of our 22 unclosed cavities following paraffin pneumonolysis. In 4 cases there was no measurable shift, in three it was from 1 to 2 cm., in five from 2 to 3 cm., in five from 3 to 4 cm., in two from 4 to 5 cm., in two from 5 to 6 cm., and in one from 6 to 7 cm. These figures represent 15 anterior and 7 posterior pneumonolyses.

The complications of the operation include the 2 cases of fatal operative tear of the lung which have already been discussed in this article. In 3 cases the operation was apparently responsible for a spread of the tuberculosis; this was in the base of the lung of the operated side in one case, in the base of the contralateral side in one case, and in the apex of the contralateral side in one case. The present prognosis is unfavorable in two and favorable in one. There was bilateral tuberculosis before operation in all cases and it was exudative in character. Incidentally, thirteen of the 43 cases in this series had predominately exudative lesions; the clinical results were poor in nine and good in only four.

In one patient there was more than the average amount of bleeding during separation of the parietal pleura from the thoracic wall, but the wound was perfectly dry at the time that the paraffin was introduced. Thirty-seven hours after operation there were signs of increasing intrathoracic pressure and the incision was then reopened, the paraffin and fresh blood clots removed, and the extrapleural space filled with gauze. The bleeding did not recur and fourteen days later an extrapleural thoracoplasty was performed; the patient's cavity is closed and her sputum is negative. In one patient there was a mild staphylococcus infection of the skin and subcutaneous tissue of eight days' duration; it did not involve the muscles, the paraffin remained in place, and the cavity is closed. In one patient, whose incision remained solidly healed for six months, a small sinus then formed in the incision and approximately 25 gm. of the total filling of 325 gm. was discharged during eight months, and then the sinus closed and has now remained closed for eleven months, during which time the patient has been well and doing full-time medical work. Two patients began to expectorate paraffin months after operation. In one of them this followed progression of the tuberculosis in the opposite lung and occurred seven months after operation; a few short match-stick-sized pieces of paraffin have been expectorated. The second patient, who still has an open cavity and positive sputum but whose tuberculosis has been improved since operation, began to expectorate similarly sized pieces of paraffin eighteen months after operation and has continued to do so during several months.

Two patients had symptoms of intercostal neuritis for several days, beginning a few days after operation; the symptoms have not recurred. In 8 patients there was considerable temporary dyspnoea, and in four mild postoperative dyspnoea; in none did this symptom persist. The usual postoperative febrile reaction was from 100° to 101° for three or four days; in no patient did the preoperative temperature exceed 100

degrees. The average gain in weight in the improved cases was 15 lbs. and the average loss in the unimproved cases was 10 lbs. Two patients, both with unclosed cavities, had haemoptysis four and seven months, respectively, after operation. In one patient there was a small temporary postoperative axillary effusion and in none was there sinking or migration of the paraffin.

SUMMARY

1. Although we have long been prejudiced against introducing a foreign-body permanently into the tissues, two years ago we began to use paraffin pneumonolysis for patients whose prognosis was hopeless if this operation were not used.

2. In the past two years we have employed it forty-three times. In 3 patients a thoracoplasty might safely have been used in its place. In 3 others, very recent active tuberculosis in the contralateral lung made thoracoplasty a greater than average risk. In 37 patients thoracoplasty was definitely contraindicated, chiefly because of extensive bilateral tuberculosis.

3. The tuberculosis in 69.9 per cent of the patients has been arrested or improved, and 30.1 per cent are unimproved or dead. Six of the patients whose disease did not become arrested subsequently had a thoracoplasty, and four of them are practically well, one is greatly improved, and one is dead.

4. In the 29 cases in which extrapleural adhesions did not prevent the surgical formation of an adequate extrapleural space to receive the optimal amount of paraffin, 68.9 per cent of the cavities became closed, whereas, in the 14 cases in which the extrapleural cleavage was unsatisfactory, only 7.1 per cent of the cavities became closed.

5. The results in those cases in which the posterior approach was used are superior to those in which the anterior approach was used. Extrapleural cleavage was satisfactory in 89.5 per cent of the posterior operations and in only 50 per cent of the anterior operations. Among the patients with satisfactory cleavage, the cavities became closed in 76.5 per cent of the cases that had had the posterior operation and in 58.4 per cent of those having had the anterior operation.

6. Although paraffin pneumonolysis is a less effective operation than a properly performed thoracoplasty and is subject to several complications, it produces many perfect results and is virtually indispensable for certain cases in which all other therapeutic measures that might be expected to arrest the tuberculosis have been tried or are contraindicated.

BILATERAL COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS[1,2]

WILLIAM C. POLLOCK[3]

Bilateral compression or collapse therapy applied to pulmonary tuberculosis is a warranted, logical and successful procedure.

In comparison to the large group to which unilateral collapse is applicable, bilateral collapse has an applicability to a more or less limited group of cases.

The utilization of bilateral collapse therapy is the logical result of the evolution of collapse therapy.

The value of unilateral collapse in the treatment of pulmonary tuberculosis has been definitely established. Progress is yet to be made in the more immediate application of collapse therapy. Routine rest treatment has so often failed, even in minimal or moderate involvement, that one should resort to collapse therapy without an unjustifiable delay. The success or failure of an institution may well be judged by its utilization of collapse therapy. Judgment may be passed not only upon the instances of this type of therapy, but also as to any unwarranted duration of routine treatment prior to the induction of collapse or compression.

As expressed by Burrell (1), "If artificial pneumothorax can save the lives of many patients who have failed to improve under routine rest treatment, how many more would it save if employed in the earlier stage of the disease before pleural adhesions have formed, and while the disease is more definitely unilateral?" He states that when once one is able to diagnose the condition by physical signs the case cannot then be regarded as in an early stage of the disease, and certainly pneumothorax therapy should be advocated. It is only a waste of time to try routine rest treatment because, although a few do well, many do not, and, even for the few who do well, the improvement is only temporary as relapse usually follows.

[1] Read at a joint meeting of the Denver County and El Paso County (Colorado) Sanatorium Associations, February 17, 1933.

[2] Published by permission of the Surgeon-General, U. S. Army, who is not responsible for any opinion or conclusions drawn herein.

[3] Major, Medical Corps, U. S. Army, Medical Service, Fitzsimons General Hospital, Denver, Colorado.

The viewpoint of Burrell is a logical one and a viewpoint entertained by numerous phthisiologists, and by a vast majority when cavitation is present.

Bethune (2) expresses our viewpoint for, in speaking of cavitation, he states, "Any optimism as to the outcome in cavity cases when treated conservatively is unjustifiable."

Frequently an attempt has been made to institute collapse therapy after an unreasonable delay. Often the physician regards the insidious progress of the disease apathetically. Usually there has been nothing particularly dramatic about the onset of the disease, and the physician's mode of action has been just as undramatic.

A great surgeon once said, "Observe appendicitis, appendix in hand." Some tuberculosis specialists should say, "Observe pulmonary tuberculosis with the involved lobes partially collapsed or compressed."

The fate of patients with cavitation is very well shown by the study of Barnes and Barnes (3) who report the outcome of 1,454 cavity cases in which they found a mortality of 80 per cent within one year, of 90 per cent within five years, and an average duration of life of 15.8 months. Sprungmann's (4) study also clearly demonstrates the fate of patients with cavitation. His study included 626 cases. In contrast to the above study, Neuberger reports 86 cases of pulmonary tuberculosis among laborers treated by artificial pneumothorax. He states that after one to five years 61.6 per cent had regained and retained their working and earning ability, whereas only 21.1 per cent were incapacitated and 17.4 per cent had died. When cavitation is present, suspected or prognosticated, collapse therapy is demanded.

We are aware that pulmonary tuberculosis in far-advanced stages does heal spontaneously; but in observing these cases one should not be misled by the few exceptions. Cavities heal spontaneously for, as stated by Pinner (6), every experienced phthisiologist has observed spontaneous closure of cavities. We (7) reported the spontaneous closure of cavities in 40 cases collected over a period of one year, but comprising the admissions over a period of several years. In considering the great groups of cases surveyed we consider this number of spontaneous closures insignificant.

Originally unilateral collapse consisted only of induced pneumothorax, but often this procedure was unsuccessful because of pleural adhesions or an adherent lung. Unsuccessful or unsatisfactory results by pneumothorax demanded other forms of collapse therapy to care for this case

group. Phrenic exairesis, thoracoplasty, oleothorax and intrapleural pneumolysis with cauterization of pleural adhesions appeared as adjuvants or forced substitutes for unsuccessful pneumothorax. The evolution of collapse therapy has increased greatly the size of the case-group to which collapse therapy was applicable. Often the resort to the more radical types of collapse therapy was the result of delay in instituting pneumothorax sufficiently early prior to the formation of pleural adhesions.

These procedures, applied singly or in conjunction with one another, fully care for unilateral cases. Unilateral collapse after many years has become accepted as the treatment of choice and in what we term suitable cases.

Experience soon taught us that the contralateral lung need not be so relatively uninvolved. As stated by Bronfin (8), "Experience has since shown that proliferative and even fibro-caseous processes in the so-called better lung, when not too extensive, improve after a satisfactory collapse of the more involved lung has been obtained." This observation doubtless led to the development of the expansile or selective type of induced pneumothorax so as to widen the field of usefulness of the procedure, in that less radical collapse warranted its use in the presence of greater contralateral disease.

We have in collapse therapy a method of arresting the disease-process in a great group of cases, a development of which the profession should be justly proud, proud not only for its effect upon our patients, but because of the elimination of open cases of tuberculosis with a beneficial effect upon our future generations.

We are now confronted with a group of patients who because of too extensive bilateral involvement are unable to undergo treatment by unilateral collapse. Many cases neglect their symptoms or are treated for some other condition, other than pulmonary tuberculosis, during which period there has been progressive disease. What is to be done for this large group? Do we hope to bring about an arrest of their bilateral disease by routine rest-care since we admit defeat by utilization of this method in relatively unilateral cases? We cannot hope to do so, for without definitive treatment this large group of cases can usually expect only some prolongation of life, followed by retrogression and early death.

We advocate for this group definitive treatment in the form of bilateral collapse therapy applied in its various combinations.

The types of bilateral collapse we have used are as follows:

1: Bilateral artificial pneumothorax.
2: Pneumothorax with contralateral phrenic exairesis.
3: Thoracoplasty with contralateral pneumothorax.
4: Oleothorax and pneumothorax contralaterally.

There are other combinations, such as thoracoplasty and contralateral phrenic exairesis, and bilateral thoracoplasty with case-groups too small to be conclusive.

In bilateral involvement just as in unilateral involvement we consider pneumothorax the treatment of choice. Generally this method of collapse is first attempted before other procedures are used. In our bilateral-pneumothorax cases, for convenience of discussion, we had divided our cases into three groups:

1: Group-one cases consist of moderately recent cases that present themselves for treatment with bilateral involvement sufficiently extensive to preclude unilateral collapse therapy. The cases of this group may or may not have cavitation.
2: Group two consists of cases with disease of longer duration. Usually these cases have attempted arrest of their disease by routine rest-cure; but unfortunately they now present bilateral cavitation. Parenchymal nodose lesions may or may not be well fibrosed. Bilateral pneumothorax is instituted primarily for the closure of cavitation.
3: Group three consists of cases that develop a bronchogenic spread or present a reactivation of lesions once thought to be quiescent in the contralateral lung during unilateral-pneumothorax therapy. Because of this complication pneumothorax is induced contralaterally and the pneumothoraces are carried on simultaneously.

In groups one and three a small expansile type of pneumothorax is usually sufficient on the lesser-involved lung. In group two difficulty in obtaining cavity compression is encountered because of fibrosis and more compression is usually necessary. Pleural adhesions are troublesome and frequently one is unable to gain the pleural space on one side. Pleural adhesions, of course, may be a factor of failure in any of the above groups.

Last year we reported results of bilateral pneumothorax in 25 cases. In this group of cases we were dealing largely with failures obtained by routine treatment. They were chiefly patients who had been denied the advantage of collapse therapy because of too extensive bilateral disease. In this group we obtained unsatisfactory collapse on one side in 11 cases

because of pleural adhesions. Thirteen cases showed satisfactory collapse of both lungs. One case showed unsatisfactory collapse bilaterally. Since this report we have instituted bilateral pneumothorax in 34 additional cases with better results More successful results were obtained because of earlier emp oyment of the procedure.

In our first study we learned of the value of bilateral pneumothorax, and results were achieved even when applied late in the disease, often showing progression of disease. More recently we have attempted to apply the procedure earlier, and results have been much better. In cases in which bilateral collapse by pneumothorax is contemplated it is even more important to institute pneumothorax at an early date than is often true of unilateral collapse. The disease is so often extensive with more chance of there being subpleural lesions, which, of course, favor the formation of pleural adhesions.

The use of bilateral pneumothorax takes care of a large group of cases suffering from bilateral involvement when unilateral collapse is precluded. Though complications are more often encountered and are of a more severe nature, though results are frequently only such as to prolong life, yet arrest of the disease is brought about in a sufficiently large group to demand its use. Cases that do best are those with the pulmonary bases adherent to the diaphragm. In longer-standing cases in which parenchymal nodose lesions have become arrested, leaving bilateral cavitation, the cavities may be eradicated by bilateral pneumothorax. Rapid fatal termination by death because of a bronchogenic spread in the contralateral lung during unilateral pneumothorax may be prevented by pneumothorax applied to the contralateral side carrying on the two pneumothoraces simultaneously. In cases in which an unsuccessful or unsatisfactory collapse is obtained on one side, treatment may be continued until there is sufficient improvement in one lung to warrant more radical surgical collapse in lieu of the unsatisfactory pneumothorax. In this event it is wise to continue the successful pneumothorax as an expansile type. Bilateral pneumothorax has thus made possible the utilization of surgical collapse once impossible because of extensive bilateral disease.

Results in cases of this character cannot, in general, be startling as to immediate or final results. In some instances, however, rather startling results have been obtained. In bilateral collapse we have noted the rapid clearing of lesions, or the rapid apparent obliteration of cavitation, as is so frequently observed in unilateral pneumothorax.

After my discussion of bilateral pneumothorax the following questions were presented:

1: What is the interval of induction of the two pneumothoraces?
2: Do you attempt to maintain the hemithoraces at about the same intrathoracic pressure?

In lieu of case-reports it is thought advisable to discuss briefly the above questions. As to the interval of induction between the two hemithoraces, we may state that it is an individual problem, there being no set interval. The general plan is to obtain a satisfactory expansile type of pneumothorax on the greater-involved side first. This is continued until gas refills are required at weekly intervals. Then pneumothorax is induced on the contralateral side; this latter pneumothorax will require more frequent refills, but soon refills are given alternately at weekly intervals. Should both lungs present equal massive involvement, the interval of induction of the two pneumothoraces is shortened to prevent further spread or cavitation. Extra strain upon a lung presenting lesions destructive in type may soon progress if uncompressed.

The initial pneumothorax may be performed upon the lung showing rather less parenchymal involvement should the lung show extensive cavitation. It is considered important to eradicate the potential dangers of cavitation as soon as possible.

The following tabulation presents some data in reference to bilateral pneumothorax:

Name	*Age*	*Date of Induction*		*Greater-Involved Lung*	*Site of Cavitation*
		Right	*Left*		
A. P.	25	1– 5–32	12–11–31	Left	Multiple, large, right upper lobe
J. M.	34	2–25–32	2–19–32	Equal bilaterally	Small, multiple, both upper lobes
H. P.	27	12–18–31	5–13–32	Right	Upper, lobe, right
H. P.	20	9–27–32	10– 7–32	Approximately equal involvement	Cavitation, moderate, both upper lobes
E. M.	39	3–19–32	3–15–32	Left	Large, left; smaller one on right
J. W.	36	11– 2–32	11– 3–32	Bilateral haemorrhage Equal bilaterally	Small cavitation, both uppers
M. W.	36	1–27–32	2– 4–32	Equal involvement	Extensive diffuse involvement, no cavitation
P. D.	38	12– 2–32	11– 1–32	Left	Large cavity, left upper

Name	Age	Date of Induction		Greater-Involved Lung	Site of Cavitation
		Right	Left		
G. H.	37	11– 4–32	9–21–32	Left	Cavity, left upper
H. J.	22	12– 2–32	11– 1–32	Left	Cavity, left upper
E. L.	32	1–10–33	12–28–32	Left	Small, multiple cavities bilaterally
W. D.	30	11– 8–32	11–15–32	Right	Cavitation, large, bilaterally
T. T.	42	11–16–32	11– 2–32	Left	Large cavity, left upper; small multiple, right upper
J. T.	29	1–27–32	1–18–32	Approximately equal	Small, right; more destructive lesions left
J. P.	27	8–12–32	6– 7–32	Left	Left
M. T.	25	8–21–31	11–17–31	Right	Right upper

As to the intrathoracic pressures of the two sides, this, too, varies with each individual. The two sides are maintained at constant negative pressures, as both pneumothoraces are carried on as of the selective or expansile type, if possible. Should one side present massive involvement with cavitation, with slight to moderate midlung bronchogenic spread in the contralateral lung, then a greater difference in compression is demanded. In this event, the more-involved lung is rather greatly compressed and the lesser-involved lung carried on as an expansile type. There may be considerable difference between the two hemithoraces as to intrathoracic pressure without discomfort to the patient. Equal pressures are ideal; but often not possible due to the object in view. In the presence of a rather mobile mediastinum causing discomfort during the unilateral pneumothorax, symptoms disappear after induction of pneumothorax in the contralateral hemithorax.

PNEUMOTHORAX AND CONTRALATERAL PHRENIC EXAIRESIS

Pneumothorax with contralateral phrenic exairesis is another type of bilateral collapse therapy. This type of collapse may be used as the method of choice or employed because of inability to induce pneumothorax upon one side. If phrenic exairesis is selected as being a more logical procedure, it is because of the character and distribution of pulmonary lesions. The phrenic-nerve extirpation is done on the lesser-involved side.

In instances of bilateral disease, an attempt to induce pneumothorax on the more-involved side may be unsuccessful. In this event, a phrenic operation is done and pneumothorax is instituted on the lesser-involved

side. This procedure is intended to arrest the disease of the better lung, during which interval the disease of the more massively involved lung remains stationary or improves. If this proves successful, more radical surgical collapse is applied on the side of diaphragmatic paralysis. Other case reports cover this procedure.

THORACOPLASTY AND CONTRALATERAL PNEUMOTHORAX

In cases of bilateral involvement with one lung massively involved and showing cavitation, as stated, pneumothorax may be unsuccessful upon the greater-involved side. Thoracoplasty is indicated, but cannot be performed because of activity of the opposite lung. Pneumothorax therapy is applied to the lesser-involved lung to arrest the disease of the better lung. Simultaneously, there should be paralysis of the diaphragm on the massively involved side in an attempt to control progression of disease.

When the better lung shows satisfactory improvement, pneumothorax refills are given in smaller amounts and, less frequently, until a definite selective type of compression is obtained. When this has been accomplished, a thoracoplasty is performed on the opposite hemithorax, continuing the contralateral pneumothorax.

This seemingly radical type of bilateral collapse is possible because of the use of an expansile type of pneumothorax and a less radical type of thoracoplasty. Thoracoplasty is of the extrapleural perispinal upper phase with gauze pack (Casper (10)).

The case-report of *W. R.* illustrates the above procedures.

ARTIFICIAL PNEUMOTHORAX AND OLEOTHORAX

In bilateral pneumothorax obliterative pneumothorax is not an infrequent complication. When obliteration of the pneumothorax space is evident, oleothorax is induced immediately, in order to prevent reëxpansion of the lung known in Matson's (9) classification as the "inhibition type." In this type of oleothorax we use sterile paraffin oil or one per cent gomenol in paraffin oil. We have never selected this type of bilateral collapse therapy as the type of choice; but, as stated, we only institute oleothorax because of obliterative pneumothorax of one side in cases initially having bilateral pneumothorax.

In obliterative pneumothorax there is usually an acute pleurisy with exudation. The exudate soon shows a tendency to become encysted and numerous new adhesions begin to form. It is very difficult to aspirate

the exudate in its entirety due to encystment, and with the introduction of oil a tuberculous purulent exudate is apt to form. Purulent exudate must be detected early, and the inhibition type of oleothorax converted into the "disinfection type" (Matson), using gomenolized oil of a greater strength, usually 5 per cent. This line of procedure carried out energetically will soon clear up the purulent exudation. The case can then again be carried as an inhibition oleothorax.

The disinfection type may be instituted as the initial type of oleothorax in empyema complicating bilateral pneumothorax. Empyema may follow a spontaneous pneumothorax superimposed upon the artificially induced pneumothorax. Empyema may be a complication of intrapleural pneumolysis with cauterization of pleural adhesions. In either event, disinfection oleothorax is induced.

The case-report of *R. Mc.* demonstrates the use of pneumothorax and inhibition oleothorax. That of *A. P.* is of pneumothorax and disinfection oleothorax.

CONCLUSIONS

1. Bilateral pneumothorax as a type of compression therapy is a successful procedure. We have used this type of compression therapy in 59 cases during the past three years. It has taken care of a great group of cases in which unilateral collapse is precluded or there has been a midlung bronchogenic spread in the contralateral lung during unilateral pneumothorax therapy.

2. Pneumothorax, with contralateral phrenic exairesis, while applied to a lesser group has an applicability. Whether or not this type of bilateral compression therapy is used as the one of choice, depends, of course, upon the character and distribution of the contralateral lung pathological process.

3. In cases presenting a massively involved lung with cavitation in which the pleural space can not be gained, and presenting opposite lung activity too extensive for thoracoplasty, the following procedure is recommended: Phrenic exairesis upon the massively involved side, artificial pneumothorax upon the contralateral side, later a thoracoplasty upon the massively involved side, continuing the contralateral pneumothorax as an expansile type.

4. Obliterative pneumothorax is not an infrequent complication of bilateral artificial-pneumothorax therapy. When obliteration of the pneumothorax space is evident, the inhibition type of oleothorax is in-

stituted to prevent reëxpansion of the lung. Satisfactory compression may be maintained by this procedure.

5. Empyema complicating bilateral pneumothorax or following ntrapleural pneumolysis is treated by disinfection oleothorax. The immediate institution of disinfection oleothorax in tuberculous empyema yields very satisfactory results. Treatment must be immediate and energetic.

6. The above combinations of collapse or compression therapy have been developed during the evolution of collapse therapy, and have greatly increased the case-group to which definitive treatment may be applied. The once greatly limited field of collapse therapy has been broadened to a field with practically unlimited possibilities. Our failures and the severe complications encountered are overshadowed by successful results. We advocate bilateral collapse and are continuing our work with great optimism.

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CASE REPORTS

Thoracoplasty—Contralateral Pneumothorax

W. R., white, male, age 25. Admitted with far-advanced pulmonary tuberculosis. Right lung extensively involved with 3 x 4 cm. cavity, right upper. Bronchogenic spread on left, with nodose lesions extending well into periphery. Collapse therapy demanded for cavity-closure on right, but judged to be precluded because of contralateral disease. Bilateral pneumothorax attempted, but unsuccessful on right. Phrenic exairesis performed on right, followed by upper-phase thoracoplasty with gauze-pack. This latter procedure was not performed until lesions in left lung were thought to be quiescent.

Table of collapse therapy

Procedure	*Location*	*Date*
Attempted pneumothorax	Right	July 27, 1931
Phrenic exairesis	Right	August 11, 1931
Pneumothorax	Left	November 17, 1931
Thoracoplasty	Right	March 12, 1932

Result: Disease process arrested in both lungs. Patient takes daily graduated exercise without symptoms. He leads practically a normal life. No cough or sputum, no temperature.

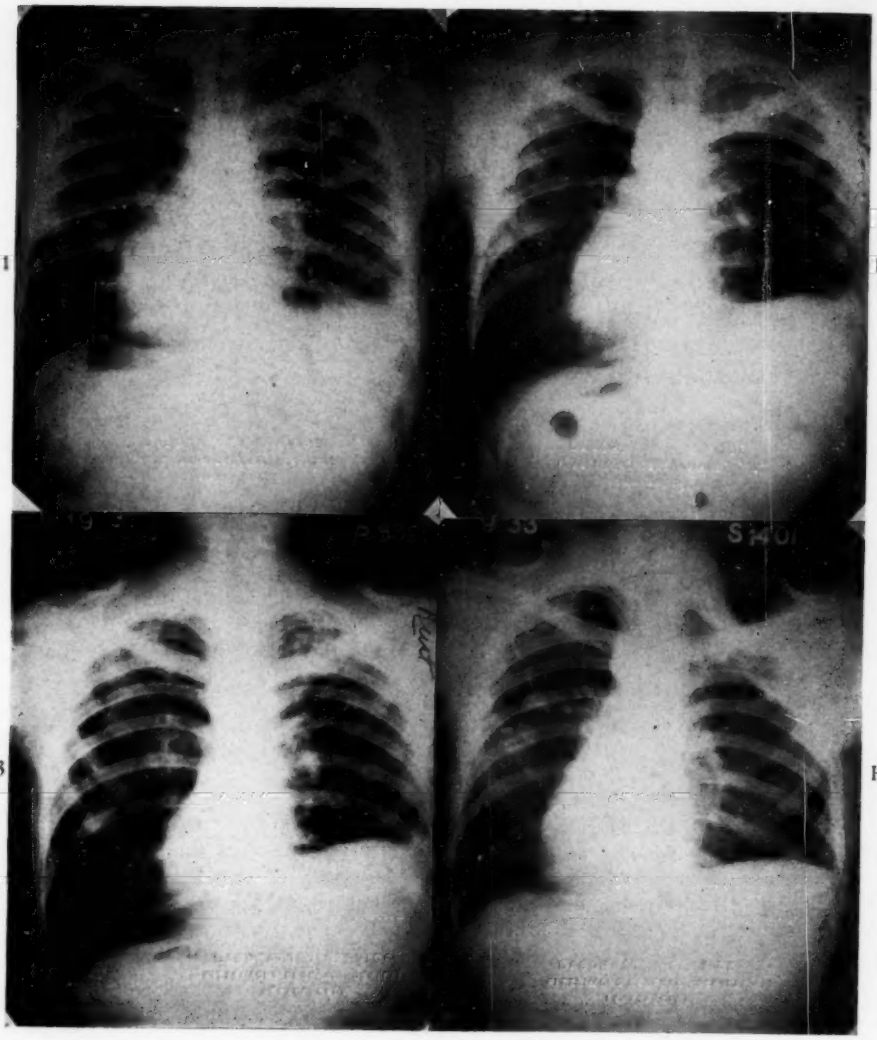

FIG. 1. *W. R.* upon admission, April 17, 1931. Large cavity, right upper lobe.

FIG. 2. *W. R.* Right phrenic exairesis, October 24, 1931.

FIG. 3. *W. R.*, November 19, 1931: right phrenic exairesis; left artificial pneumothorax.

FIG. 4. *W. R.*, January 9, 1933: left pneumothorax; right thoracoplasty, done March 12, 1932.

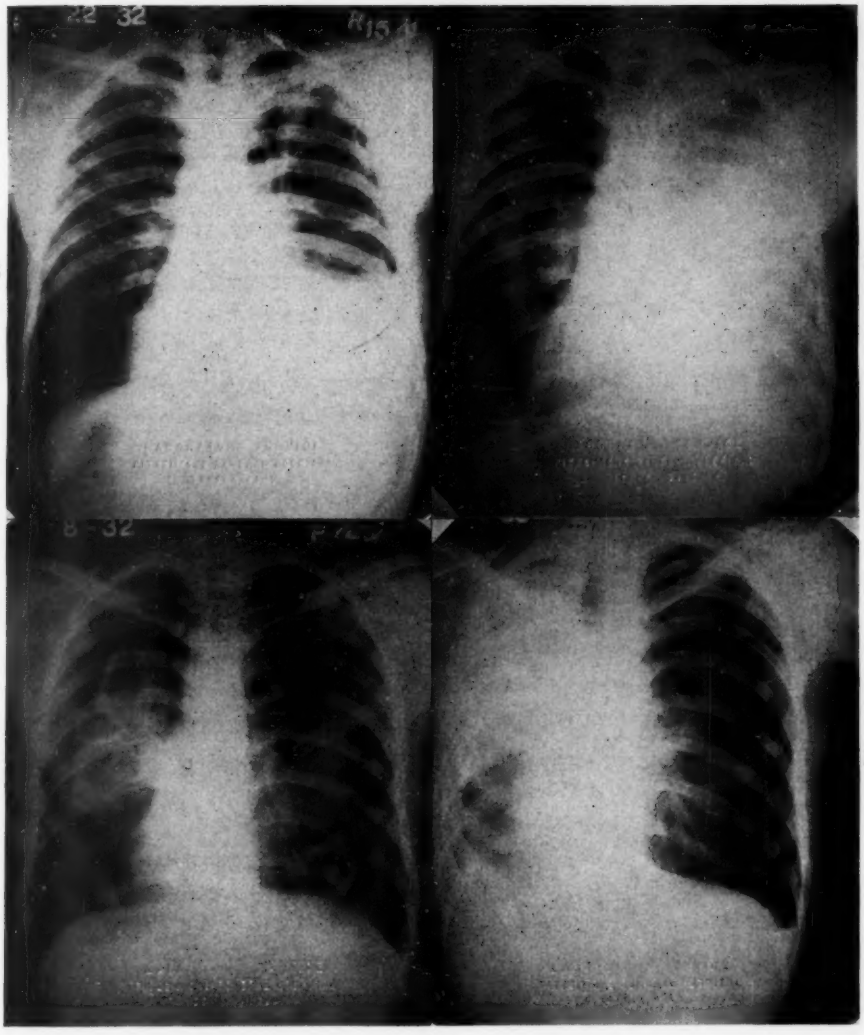

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 5. *R. Mc.*, April 22, 1932. Bilateral tuberculosis: right pneumothorax with serous effusion. Obliterative pneumothorax was soon evident.

FIG. 6. *R. Mc.*, February 1, 1933. Left pneumothorax, with marked clearing of lung. Complete right oleothorax.

FIG. 7. *A. P.*, January 8, 1932. Bilateral pneumothorax. Pleural band-adhesion, 1st costal i.s. Film taken prior to intrapleural pneumolysis, which was followed by pyopneumothorax.

FIG. 8. *A. P.*, February 1, 1933. Right pneumothorax for over one year. Disinfection oleothorax, left for one year. Purulent exudate no longer present. Forty-two aspirations required during one year.

Pneumothorax—Inhibition Oleothorax

R. Mc., white, male, age 29. Admitted February 18, 1932, with bilateral involvement, with cavitation in right upper. Bilateral collapse therapy indicated; so pneumothorax induced on both sides. Pneumothorax on the right complicated by pleurisy with effusion, which soon showed evidence of obliteration of pleural space. Before complete obliteration of space, inhibition oleothorax, using sterile paraffin oil, was instituted. Pneumothorax on right not satisfactory because of pleural adhesions and adherent upper lobe.

Table of collapse therapy

Procedure	*Location*	*Date*
Pneumothorax	Right	March 11, 1932
Pneumothorax	Left	April 22, 1932
Oleothorax	Right	June 6, 1932

Result: This case has not been under treatment very long but certainly a progression of his disease has been prevented. There has been continual clinical improvement. Prognosis good.

Pneumothorax—Disinfection-Type Oleothorax

A. P., white, male, age 25. Admitted November 28, 1931. Had rather massive involvement of left lung with midlung bronchogenic spread in the right lung. Temperature 100–101°, rapid pulse, cough, considerable sputum, loss of weight, etc. Little evidence of resistance to the disease. Immediate collapse therapy indicated. First bilateral pneumothorax instituted with benefit. Patent cavity on the left, because of pleural adhesions; otherwise pneumothorax successful on both sides. Intrapleural pneumolysis, with cauterization of the adhesion was followed by temporary bronchopleural fistula resulting in severe pyopneumothorax. Disinfection oleothorax, using 5 per cent gomenolized oil, instituted immediately. Pneumothorax on right continued.

Table of collapse therapy

Procedure	*Location*	*Date*
Pneumothorax	Left	December 11, 1931
Pneumothorax	Right	January 5, 1932
Intrapleural pneumolysis	Left	March 21, 1932
Oleothorax	Left	March 24, 1932

Result: Right lung disease arrested. Left lung satisfactorily compressed by oleothorax. Gain of 30 lbs., fever-free and ambulatory. Multiple procedures of collapse therapy in this case prevented a rapid fatal termination.

PATHOLOGICAL FINDINGS AND PATHOGENESIS OF CONGENITAL TUBERCULOSIS[1]

MORRIS SIEGEL

Ever since the reviews of congenital tuberculosis by Gaertner (39) and by Hauser (40) about forty years ago, it has been commonly accepted that the usual if not the only site of the most extensive lesions is in the liver and the regional portal lymph nodes. These findings have been attributed to the peculiarities of the foetal circulation, in which the liver is the first large receptor of maternal blood from the placenta while the pulmonary circulation is slight, the blood being shunted through the *ductus arteriosus* into the aorta.

But cases of congenital tuberculosis have been reported with disseminated involvement marked in the lungs as well as in the liver, and several instances in which the lesions were limited to the lungs and the regional pulmonary lymph nodes. The findings in these cases in which involvement is restricted to or predominant in the lungs have been attributed to the passage of tubercle bacilli through the *ductus venosus Arantii* or to the aspiration of tuberculous amniotic fluid or tuberculous matter present in the birth-canal.

Practically, therefore, congenital tuberculosis may be defined as tuberculosis in which the infection occurs before birth by way of the bloodstream (umbilical vein) or at birth by the aspiration of tuberculous amniotic fluid or tuberculous matter present in the birth-canal. An essential difference between congenital and acquired tuberculosis is in the time when infection occurs; the term *acquired* refers to postnatal infection, while the term *congenital* refers to infection occurring before this postnatal period. Theoretically, the eye, mouth and respiratory tract above the level of the glottis might be involved during intrauterine life by contact infection with tuberculous amniotic fluid, or the gastrointestinal tract by the ingestion of infectious amniotic fluid, but actually no such proved cases have been reported.

The proof of congenital origin depends upon the nature and location of

[1] From the Pathological Institute of the Wiedener Krankenhaus, Vienna, Austria (Prof. Dr. Carl Sternberg, Director).

the lesions and on the isolation of the child immediately after birth from its tuberculous mother and from all other sources of infection. If the oldest and most marked lesion is in the liver and portal lymph nodes, the infection occurred through the umbilical vein and is therefore undoubtedly congenital. This same vascular route also carries infection which produces lesions in other organs, for instance, spleen or lungs, usually with involvement of the liver. This portal has been used by some to explain involvement of the lungs only, by the passage of the tubercle bacilli through the *ductus venosus Arantii*. Furthermore, repeated infection in one or more organs may occur by recurring blood-stream dissemination before birth from sources in the placenta or after birth from the infant's own lesions. And the aspiration of infective amniotic-fluid or postnatal infection by aspiration or by ingestion may occur in these infants already infected through the blood-stream. Accordingly, the final results may represent differences in the time and even in the route of infection.

But primary or predominant lesions in the lungs, especially when limited almost entirely to the lungs and the pulmonary lymph nodes, introduce doubt as to the tuberculosis being congenital, because of the difficulty in ruling out acquired, that is, postnatal infection. In such cases however, the clinical course and the pathological findings (intensity, nature and distribution of the tuberculous process) in the infant, the presence of advanced tuberculosis in the mother usually dying of tuberculosis soon after delivery, and the isolation of the child immediately after birth in a nursery aid in dispelling doubt. The isolation of a child in a nursery does not in itself rule out the possibility of postnatal infection, for the child is not in hermetically sealed surroundings. And this possibility of postnatal infection obviously becomes more probable the longer the child lives. So that cases, like those of Kochmann (37) and of Sitzenfrey (38), always separated from their tuberculous mothers in a nursery but dying at five and at six months of age with pulmonary lesions and primary complexes in the lungs similar to those found in acquired tuberculosis, are less certainly congenital than similarly isolated cases of Siegel (8) and of Harbitz (12), dying at nineteen and at twenty-five days of age with diffuse pulmonary lesions of the same pathological nature throughout the lungs and unaccompanied by a localized primary complex of the type found in postnatal infections.

The cases chosen include one nine-months stillborn and 37 newborn infants, either isolated directly after birth, or with primary or most exten-

TABLE 1

Table of cases and of the more frequently involved organs

CASE NUMBER	AGE	PART A COMPARISON OF LUNG AND LIVER INVOLVEMENT			PART B INVOLVEMENT OF MORE FREQUENTLY AFFECTED ORGANS					PART C LYMPH NODES MORE FREQUENTLY AFFECTED		
		Lung lesions predominant	Liver lesions predominant	Both equally involved or no difference specified	Lung	Liver	Spleen	Gastrointestinal tract	Kidney	Pulmonary	Mesenteric	Portal
1	still-born	x			++	m	m		++			
2	1 day			x	++	++	++		+−	c	c	c
3	2 days		x		++	++	++	−		c	ct	c
4	few days		x		+	++	++					
5	12 days	x			++	m						
6	14 days			x	++	++					c	c
7	15 days		x		++	++	++					
8	19 days	x			++	m	m	−	−	a	b	−
9	19 days	x			++	++	−	−	+−	−	e	
10	19 days	x			++	−	−			b	b	b
11	20 days	x			++	−	−			c		
12	25 days	x			++	−	−			c		
13	26 days		x		+	++	++	−	+−	ct	c	c
14	29 days	x			++					c	−	−
15	30 days		x		−	++	++		−		e	
16	31 days			x	++	++	++		++	c	c	
17	34 days	x			++					c		
18	37 days		x		++	++	+	?			ct	c
19	39 days			x	++	++	++	u	++	c	c	c
20	48 days			x	++	++	++	t		c	c	c
21	52 days			x	++	++	++	u			c	c
22	52 days			x	++	++	++	ut	+	c	c	c
23	54 days	x			++	++	++		+−	c	−	−
24	51 days		x		++	++	++		++	c		c
25	60 days			x	++	++	++	t	++	ct	ct	c
26	68 days			x	++	++	++			c		
27	70 days			x	++	++	++	u	++	c		c
28	84 days	x			++	++	++	u		c	c	
29	84 days			x	++	++	++	u		−	c	c
30	86 days	x			++	m	m	−	−	c	a	
31	2 mos. 3 wks.	x			++	−	++	−	−	c		
32	3 mos.	x			++	m	++			c	c	
33	3 mos.	x			++	++	++	u	+	c	c	
34	89 days			x	++	++	++	u	++	c	c	c
35	96 days	x			++	++	++	u	++	c	c	
36	113 days			x	++	++	++	u		t	c	c
37	153 days	x			++	−	−	u		c	c	
38	6 mos.	x			++	++	+	u	+	c	c	
	Total.....	18	7	13	37	31	29	14	15	28	25	16

Note: ++, Many lesions or diffusely studded; +, moderately involved; +−, few lesions; −, no lesion; m, microscopic lesions only; u, ulcers; t, tubercles; c, caseation; ct, caseous tubercles; a, adenitis (tuberculous); e, enlargement; b, bacilli with no lesion; ?, questionable. A blank space in Parts B and C indicates that the information was not specifically mentioned in the case-report.

sive lesions in the liver. Cases, not isolated after birth and showing only diffuse lung lesions or generalized tuberculosis predominating in the lungs, were not included in the study,—with one exception, an infant twelve days old. The 38 cases chosen were all younger than three and a half months except 3 infants between three and a half and six months of age. These cases of undoubted or probable congenital tuberculosis are arranged for purposes of study in the order of the infants' age at death. (See table of cases, table 1.)

RESULTS AND DISCUSSION

Lungs: The lungs were most frequently involved. They showed macroscopic lesions in 37 out of 38 cases (97.4 per cent), or in all cases except one, thirty days old.

The macroscopic pulmonary lesions were virtually always generalized and were described as follows:

	Total cases	*Remarks*
Tubercles	34	Miliary or larger and confluent
"Bronchopneumonic areas"	2	One alone, one with tubercles
"Infiltrations"	2	Varied from miliary to 1-cm. diameter
In addition were areas of		
Calcifications	2	One, the stillborn case
Cavitations	3	In infants older than 2½ months; small and scattered in two infants; a single (2-cc. diameter) cavity in a third

Large, discrete, possibly old lesions resembling, and occasionally mentioned as primary, were recorded in 12 cases, of which four had similar lesions in the liver, usually with caseous regional lymph nodes.

It is noteworthy that the primary lesions, on account of the peculiar modes of infection in congenital tuberculosis which approximate experimental conditions, may spread diffusely through many organs by way of the vascular route, or spread throughout the lungs by the aspiration of infective amniotic fluid, an actual example of which was published by the writer under the guidance of Professor Carl Sternberg of Vienna.

A microscopic report was recorded in only 12 cases and showed:

"Tuberculous alveolitis" (pneumonic areas) and bronchiolitis	3 cases
"Tuberculous alveolitis" (pneumonic areas)	2 cases
"Tuberculous alveolitis" (pneumonic areas) and tubercles	3 cases
"Tubercles" (usually caseous)	4 cases

Therefore, microscopically the lesions were often tuberculous pneumonic areas with, or sometimes without, bronchiolitis, although macroscopically the lung lesions almost invariably resembled tubercles.

There were 7 cases with macroscopic involvement of lungs and of regional lymph nodes only; six died in the latter part of the first month and the seventh in the fifth week. This similarity in age of cases with lung lesions seems more than coincidental. This may indicate similar conditions in the time and in the mode of infection, one possibility being the aspiration of infective amniotic fluid at birth, and death so soon that disseminated infections have not had time to produce macroscopic lesions in other organs.

Liver: The belief that the liver is most frequently and predominantly involved in congenital tuberculosis may have to be modified, for the results of this study show that the liver was involved less frequently and less extensively than the lungs (see *part A* of table of cases—table 1), as summarized in the following tabulation:

	Total cases		*Remarks*
1: Frequency of lung involvement.....	37	(97.4%)	
Frequency of liver involvement.....	31	(81.5%)	
2: Lung involved without liver lesions...	7		(5 cases showed lesions in the lungs only)
Liver involved without lung lesions...	1		(No microscopic lung report)
3: Lung and liver involved together.....	30		
with (a) lung lesions predominating.	11		(5 cases with the liver lesions microscopic in size)
(b) liver lesions predominating.	6		(All with gross lung lesions)
(c) lung and liver equally involved, or no difference specified.....	13		

The extent of liver involvement varied with three age-periods. In the first or youngest group, approximately in the first two weeks of life, the liver lesions were as marked as in any other organ. And this is the only group in which the belief that liver lesions predominate in congenital tuberculosis may be applicable. For in the next age-group, in the latter half of the first month of life, macroscopic liver lesions were usually absent, and the lungs alone were most frequently involved. In the third age-group, older than one month, liver lesions were usually present, al-

ways with lung lesions that were usually equal to or more marked than in the liver; in only 2 cases were they described as less marked than in the liver.

The explanation for this peculiar grouping may lie in the time and in the route of infection and in the length of life after infection occurred. The infants in the youngest or first group died so soon after birth that they showed mainly or exclusively the effects of prepartum infection by way of the blood-stream that causes disseminated lesions. The second group shows the effects of birth with the new route, the aerogenous route, that causes initially only lung involvement, and with the circulatory changes in the liver and lungs by which the lungs become the first main receptor of venous blood with bacilli from all sources that may favor the appearance and predominance of lung lesions, as stressed by Krause (41). The infants in the third group live long enough to show disseminated involvement of liver and spleen from foci in the infant irrespective of the original routes of infection.

Although extensive tuberculous lesions in the liver and the portal lymph nodes are undoubtedly congenital, it by no means follows that intrauterine infection by the vascular route always produces lesions marked in the liver. On the contrary, the tuberculous involvement of the liver may be scanty and only microscopic in size even in repeated blood-stream dissemination, while lesions in the lungs and other organs are studded with lesions. Proof of such effects is presented by the nine-months stillborn with old and recent lesions indicative of repeated infection by way of the haematogenous route. Macroscopically, this stillborn had many "calcareous nodules" in the lungs, caseous medulla of the adrenals, numerous tubercles of kidneys, and lesions in left ovary, both lateral ventricles and thalamus. No macroscopic lesions were seen in other organs. Microscopically, the lungs and kidneys were studded with tubercles of various sizes and often caseous, while the liver had "an occasional small tubercle" and fatty changes; calcareous tubercles were found in the lung, the spleen and the pancreas, and the floor of the lateral ventricles contained an occasional caseous tubercle.

Of the 31 cases with liver lesions, there were twenty-six with macroscopic tubercles usually miliary in size, occasionally larger, and at times caseous. The remaining 5 cases, one of which was stillborn, showed microscopic tubercles. Microscopic findings, reported in 10 cases, showed tubercles in all except one, in which areas of destroyed liver parenchyma containing numerous tubercle bacilli were recorded. Localized primary

hepatic lesions were well described in two infants (cases 19 and 36); in 6 other infants, large or old-looking lesions were noted, which were associated in 4 cases with caseous portal lymph nodes.

Spleen: Splenic involvement virtually paralleled that of the liver in frequency, degree and nature of the lesions (see *part B* of table of cases—table 1) as indicated in the following summary:

	Total cases		*Remarks*
1: Frequency of liver involvement.....	31	(81.5%)	
Frequency of splenic involvement....	29	(76.3%)	
2: Liver involved without splenic changes.	3		(Two cases inadequately reported)
Spleen involved without liver lesions..	1		
3: Liver and spleen involved together...	28		
with (a) liver lesions predominating.	3		(All with gross splenic lesions)
(b) splenic lesions predominating.....	4		(Two with liver lesions microscopic in size)
(c) spleen and liver equally involved or no difference specified.....	21		

In 2 cases the lesions in the spleen were said to be more marked than in any other organ, but in no case were primary splenic lesions specifically recorded. The lesions in the spleen were described as tubercles except in one case with "diffuse necrosis;" the tubercles were usually miliary in size; they were reported as either white or yellow and occasionally as caseous tubercles. Calcification was recorded once, in the still-born infant.

Gastrointestinal Tract: Fourteen out of the 38 cases (36.9 per cent) showed tuberculous lesions. All of these 14 cases appeared in the 20 infants thirty-nine days or older, and no undoubted case of intestinal tuberculosis was reported in any of the 18 cases younger than thirty-nine days (see *part B* of table of cases—table 1); so that intestinal tuberculosis was not seen until a certain age, and was afterward reported in 70 per cent of the cases. The lungs were much involved in all 14 cases. These facts suggest, among other possibilities, the explanation of secondary infection by the ingestion of bacilli from the lungs with the production of intestinal lesions when enough time has elapsed, and when the dosage becomes great enough as occurs in experimental animals (Opie (42)).

The gastrointestinal lesions were multiple, nonulcerated tubercles in

Peyer's patches and follicles in 3 cases and one or more ulcers in 12 cases. The location of the ulcers was specified in 10 cases as follows:

	Total cases
Ileum alone	4
Ileum and colon alone	2
Ileum, colon and stomach	2
Ileum and jejunum	1
Ileum and rectum	1

So that the ileum was always involved, followed next in order by the colon. The number of ulcers varied from one in the ileum in an infant thirty-nine days old, to about sixty throughout the small intestines in an infant three months old.

Lymph Nodes: Tuberculous lymph nodes were recorded in 34 cases, usually with involvement of the pulmonary, mesenteric and portal lymph nodes in the order of diminishing frequency. Less commonly involved were retroperitoneal and cervical lymph nodes. Other lymph nodes, for instance, axillary or inguinal, were so rarely mentioned as to be of no statistical value. Caseous lymph nodes were reported once along the small curvature of the stomach, and once behind the head of the pancreas in areas of lymphatic drainage from the liver. The involved lymph nodes were enlarged, almost always caseous, with calcifications recorded in one case. In single cases only "enlarged glands" or "tuberculous adenitis" or "bacilli" (without lesions) were recorded. A tuberculous source was always present to explain the involved regional lymph nodes except in several cases of caseous mesenteric nodes without intestinal lesions. In 22 cases caseous lymph nodes were recorded in two or more regional lymphatic areas, usually a combination of pulmonary, mesenteric and portal nodes. Of these 22 cases, the location of the oldest or most marked lymphatic involvement was recorded in fourteen as follows:

	Total cases	*Remarks*
Portal nodes	11	(Either caseous mesenteric or pulmonary nodes or both were reported in these cases)
Pulmonary nodes	3	(No involved portal nodes were reported in these cases)

The relation of the primary lesion to caseous lymph nodes could not be indisputably determined in most cases because a primary lesion was not usually recorded. However this relationship can be advantageously studied by dividing the cases into four groups. In the first group of 9

cases the pulmonary lymph nodes alone were caseous, usually with diffuse bilateral involvement of the lungs alone. Here it might be safe to assume that the primary lesion was in the lungs, though a localized primary area was specifically mentioned in only one case, and in one case (no. 8) the entire bilateral pulmonary involvement was considered as primary. In the second group of 5 cases there were other caseous regional lymph nodes besides the pulmonary nodes; for instance, mesenteric in all 5 cases, and cervical in three. But the caseous pulmonary nodes were markedly involved; there were localized pulmonary areas resembling or described as primary in all the cases; and there were no caseous portal nodes. Here again one might say that the lungs were primarily involved. In the third group of 13 cases the portal lymph nodes were predominantly involved, in 11 cases with caseous lymph nodes in mesenteric or pulmonary regions or both and in two instances with "enlarged" mesenteric nodes. Localized caseous primary liver areas were specifically described in two instances and in 3 other cases a localized area was noted that resembled a primary lesion. All 13 cases had generalized disseminated tuberculosis, and in one instance (no. 19) localized caseous primary lesions were described in both liver and lung. This group represents primary intrauterine infection by way of the blood-stream (umbilical vein), with its disseminated effects and its marked involvement of the portal nodes. The fourth group was a heterogeneous one of 11 cases, which could not be classified because of lack of information. Either the involvement of the lymphatic nodes was not mentioned or caseous lymph nodes were recorded in several regional areas, usually mesenteric, pulmonary and portal, without describing their relative size or degree of involvement or the location of primary lesions.

Caseous mesenteric lymph nodes were reported in eleven out of the 14 cases with tuberculous intestinal lesions and in 7 cases without tuberculous lesions in the intestines. The possibility of primary postpartum infection by ingestion suggests itself in these cases with caseous mesenteric lymph nodes with or without intestinal lesions. In most cases the presence of lymphatic involvement most marked in the portal nodes indicates primary intrauterine infection by way of the umbilical vein. The difficulty arises in the few instances in which the mesenteric and pulmonary lymph nodes were caseous without involvement of the portal nodes and with the presence of primary pulmonary lesions. In these few cases, though the pulmonary infection was primary, one cannot tell from the reports whether the involvement of the intestines and mesenteric

nodes was also primary or secondary. That the involvement of the mesenteric lymph nodes did not always occur by ingestion of bacilli was seen in 2 cases, dying at one and two days of age, respectively, with generalized tuberculosis, including tuberculous mesenteric lymph nodes without intestinal lesions. In these cases the route of infection to the drainage areas of the mesenteric nodes was probably haematogenous, for the infants died too soon after birth for the ingestion of bacilli to cause caseous lymph nodes.

Kidneys: These were macroscopically involved with multiple tubercles in 15 cases (39.6 per cent); all of the cases had general miliary tuberculosis.

Brain and Meninges: These were not often mentioned. Tuberculous lesions were recorded in three infants. One was a stillborn, with "occasional caseous tubercles in the floor of both lateral ventricles" and in the thalamus; the second was fifty-two days old with a *hanfkorngrosse* caseous tubercle in the dura mater; and the third was three months old with many gray tubercles in both *fossae Sylvii*, the only reported instance that resembled acute tuberculous leptomeningitis.

This rarity of acute tuberculous leptomeningitis in cases of congenital tuberculosis is noteworthy, since tuberculous meningitis is so common among infants and children dying of acquired tuberculosis,[2] and since the route of infection of the leptomeningitis is said to be by way of the bloodstream, the very route by which many of the cases of congenital tuberculosis were initially infected. Interesting in this respect are the reported findings of Rich and McCordock (43) that enough bacilli do not enter into the subarachnoid space by way of the vascular route to produce acute leptomeningitis, that this condition is produced by the rupture of a caseous tuberculous area of the brain or meninges into the subarachnoid space or into the ventricles of the brain. According to such findings, the rarity of tuberculous meningitis in congenital tuberculosis might be attributed to death so soon after initial infection that there was not enough time for the extension of caseous foci into the subarachnoid space.

Other Organs: In several cases with disseminated tuberculosis, lesions were seen in other organs and tissues as follows:

	Total cases	*Remarks*
Skin	6	Usually as softened tubercles over trunk and extremities.

[2] Seventy per cent, or 100 out of 140 infants and children dying of tuberculosis in the past nine years at the St. Josef Kinderspital, Vienna, showed, on autopsy by Professor Carl Sternberg, acute tuberculous leptomeningitis either with or without diffuse miliary tuberculosis.

	Total cases	*Remarks*
Adrenals	3	As caseous medulla in 2 cases and tubercles in the third.
Heart	3	As tubercles in endocardium, myocardium or pericardium.
Tonsils	3	As tubercles and ulcers.
Ears	2	Caseation of middle ear and Eustachian tube in one case; purulent exudate with tubercle bacilli in the other case.
Pleural effusion	2	"Greenish-yellow" in one case; cloudly serofibrinous in other case.
Peritoneal exudate	1	Purulent, with many lymphocytes and polymorphonuclear cells.

Single cases were recorded with tubercles in the muscles, especially the intercostals; tubercles in bone-marrow, in thymus and thyroid; tuberculous ulceration of thigh to the periosteum; fistula-in-ano; caseous tubercles in the pancreas; tuberculous ulcers in the *ductus choledochus* and *ductus cysticus*; "tuberculosis" of the gall-bladder. There were no reported cases of tuberculosis of the joints.

SUMMARY

1. Thirty-eight cases of undoubted or probable congenital tuberculosis have been studied, all of them as reported by various authors exclusive of the writer.

2. The tuberculous organs in these cases were usually lungs, liver and spleen, and, after a certain age, intestines.

3. Macroscopically the lesions almost always resembled tubercles. Microscopically the lesions were reported as tubercles except in the lungs, where tuberculous pneumonic areas were not uncommon. Caseation was common; cavitation, ulceration and calcification were also mentioned. In the few cases in which primary lesions were specifically reported, they were described as localized caseous areas in the lungs or liver and in one instance as a diffuse bilateral tuberculous bronchiolitis and alveolitis with beginning caseation.

4. The lungs were most frequently involved. The degree of pulmonary involvement was usually equal to and occasionally greater than that of the liver. Less frequently, liver lesions were more marked than the lung lesions.

5. In the cases dying in the latter half of the first month of life, the lungs and regional lymph nodes were usually alone involved. Before and after this period, other organs were usually involved, especially liver and spleen and, in older infants, the intestines.

6. Involvement of liver and spleen went side by side, for the liver and spleen were almost always involved in the same cases and usually to the same degree.

7. The frequency and degree of hepatic involvement varied in three age-groups. It was most marked in cases dying in the first two weeks of life, least involved in cases dying in the second half-month of life, and usually involved in cases dying subsequently to this.

8. Tuberculous lesions in the gastrointestinal tract were seen in 70 per cent of cases thirty-nine days or older, all of which had advanced pulmonary tuberculosis. No undoubted intestinal tuberculosis was reported in infants dying before thirty-nine days of age.

9. The lymphatic nodes usually involved were the pulmonary, mesenteric and portal in the order of diminishing frequency. The degree of portal-node involvement was almost always greater than that of the pulmonary or mesenteric nodes affected in the same cases. A tuberculous source was always reported except occasionally for mesenteric lymph nodes.

10. Acute tuberculous leptomeningitis was reported in only one case.

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A TOPOGRAPHICAL LOCALIZATION OF PULMONARY LESIONS[1]

ALLAN J. HRUBY AND MINAS JOANNIDES

Localization of pulmonary lesions is quite vague in that it usually has reference to a relation of the lesion to a rib, an intercostal space, or else a relation to the midsternal, the mammary, or the axillary lines. In our routine examination we have to go over a large number of chest roentgenograms, averaging from 100 to 150 a day. We found it quite difficult to describe the localization of lesions in the lung and keep an accurate topographical relationship. We have resorted, therefore, to the following scheme which has helped us to localize pathological lesions in the lung, and maintain an accurate topographic visualization. By drawing certain lines on an X-ray plate we can easily divide the chest roentgenogram into a block-system so that an exact localization of pulmonary lesions can be seen or visualized.

The chest is divided in the right and left halves by drawing a vertical line from the interclavicular area to the xiphoid process. A horizontal line is then drawn at right angles to this line and at the lowermost point of the sternoclavicular junction. This line is extended to the edge of the chest-wall. Horizontal lines are again drawn at right angles to the midline at the lowermost portion of each second costovertebral junction, thus dividing the chest into either four or five horizontal divisions. Two more perpendicular lines are drawn on each side of the midsternal line. The outer one is drawn parallel to the midsternal line at the point represented by the edge of the chest wall coinciding with the first horizontal line. The second vertical line is drawn at a point half-way between the outermost line and the midsternal line and parallel to both of them. The chest is now divided into a definite block-system and, in order to signify the right from the left side, capital R or L is used to designate the side of the chest. Roman numerals I, II, III, IV and V are used to designate the different levels of the chest, while Arabic numerals are used to designate the spaces produced on each side of the midsternal line. Each half of the chest is now divided into three vertical sections and, count-

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ing from the midsternal line laterally, the chest is divided into three subdivisions which are designated by means of Arabic numerals. By this means one can describe lesions in the roentgenogram and show the exact topographical localization of the lesions.

An X-ray of the chest in this way is now divided into the block system and if we wish to subdivide or to designate a definite area on the block we can refer to the subdivisions of each block. Thus, we may refer to either

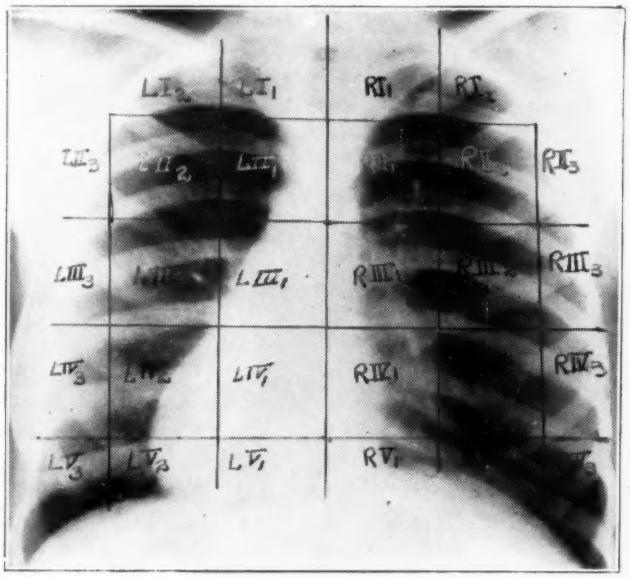

FIG. 1. TOPOGRAPHICAL LOCALIZATION OF PULMONARY LESIONS

the centre of the block or the upper right- or left-hand corner, or the lower right- or left-hand corner of the block. Thus, any of the five positions in the block may be designated as seen in the following example:

R III 2 R III 2 R III 2 R III 2 R III 2

A circle around RIII 2 would represent the centre of the block, whereas the position of the angle would represent the exact localization at each corner of the block. If a lesion is localized in an area represented by more than one block, the horizontal-division system may be utilized by desig-

nating it with the Roman numerals, as for example, RIII. A vertical subdivision of the chest may be represented by Arabic numerals, as for example, R2. This system has been used quite satisfactorily in our Clinic and has helped us a great deal, not only in the visualization of the lesions from the point of view of topographical anatomy, but also in saving a great deal of time and writing materials in making long-hand topographical descriptions for localization of lesions. We have a special form in which the usual physical signs are recorded directly on the specific portion of each block on the plate. (See figure 1.)

THE DISPLACEMENT OF INTRATHORACIC VISCERA RESULTING FROM PATHOLOGICAL PROCESSES IN THE LUNG

An Analysis of the Causes of Diaphragmatic Rise, Dextroposition and Sinistroposition of the Heart and Mediastinum[1]

MINAS JOANNIDES

Dextrocardia and sinistrocardia are distinct entities, and are frequently confused with acquired dextroposition or sinistroposition of the heart. In an excellent article on this subject Lichtman (45) discussed the literature to date on dextrocardia and classified its different types. He also made an effort to reclassify cases that had been previously reported incorrectly as cases of true dextrocardia. It may be of value to state that dextrocardia may be classified under four major groups, namely, the congenital type, the acquired type, the partial and the complete. Our interest in this subject has been aroused by the frequent displacement of the mediastinal structures and of the diaphragm in a large number of X-ray plates that have come to us for routine examination.

In the Dispensary Department of the Chicago Municipal Tuberculosis Sanitarium, which comprises 9 such dispensaries, we have a central X-ray plant, where we take the X-ray films of the chests of patients from all the dispensaries. In our scheme of considering for collapse therapy all dispensary patients at the earliest possible moment, we have gone over every X-ray plate before it is sent to each dispensary. We have a total of 55,000 patients under the supervision of our dispensary staff. This large number of patients necessitates the taking of an average of 1,000 roentgen films per month. Mediastinal displacement has been quite common on these plates and is present in 10 to 15 per cent of all films examined. Because the heart is the bulkiest organ in the mediastinum, attention has heretofore been centered primarily on the displacement of the heart. Such a displacement has been referred to as *false dextrocardia* or *acquired dextrocardia*. Hedblom (13) reported 10 such cases. He classifies as cases of acquired dextrocardia only those in which there is "a displace-

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ment to such an extent that the whole heart lies to the right of the left sternal border." He states that among the causes of dextrocardia one may consider

> pressure on the heart and mediastinum from the left, or a pull from the right. The pull to the right may be exerted by contracting bands attached directly to the pericardium, or by a shrinking lung fixed to the wall of the chest on the one side and to the pericardium on the other, but it also results from a potential vacuum produced by the contracting cicatrizing or atelectatic lung. [He further states] that it was frequently observed that the cicatrizing lung may bring about a complete dextrocardia in the absence of pleural adhesions.

We wish to emphasize the last statement because we are certain that the presence of pleuropulmonary adhesions has little, if any, bearing in bringing about intrathoracic organ displacement. Our experience with 250 such displacements which we have studied has convinced us that the potential vacuum resulting from sclerosis of one lung has been instrumental in bringing about mediastinal displacement towards the sclerotic side. This observation is of great importance in collapse therapy because some phthisiologists may consider mediastinal displacement or acquired dextrocardia as a contraindication for pneumothorax collapse. It is true that many such patients may present adhesions which prevent the induction of pulmonary collapse with artificial pneumothorax. A large number of patients with such a displacement have been readily collapsed and improved. One particular case is a very good example of this difficulty.

A nun had been under the professional care of one of Chicago's eminent phthisiologists. This patient presented a very marked mediastinal displacement to the left. She also had an extensive ulcerative lesion of the left lung with multiple cavitations. Collapse therapy was considered, but because of some involvement in the contralateral lung a thoracoplasty was considered as dangerous. Artificial pneumothorax was not considered seriously because of the marked mediastinal displacement towards the sclerotic side. The patient was, therefore, compelled to stay in bed and receive the ordinary sanatorium regimen. Following some emotional excitement the patient developed a haemorrhage and lost about one quart of blood. The Pneumothorax Clinic was called upon by the attending physician and an attempt was made to induce artificial pneumothorax as an emergency procedure. A satisfactory collapse was induced within 48 hours, so that the haemorrhage was well under control. This collapse was maintained and now, 18 months after the initial injection, the patient has had no more haemoptysis, has a negative sputum, and is up and about. The interesting feature of the roentgenograms is that there were no

symphyses between the chest-wall and the lung except one band at the apex that prevents the apex from completely dropping toward the hilum.

Up to the time of our experience with this patient one of the contraindications for induction of artificial pneumothorax at our clinic was mediastinal displacement. This case, however, has changed our attitude entirely, so that mediastinal displacement in the presence of tuberculosis is regarded as an indication for collapse therapy. Such a displacement produces a tendency toward greater lung expansion on the opposite side, and a tendency to emphysema may develop. This condition corresponds to cardiac hypertrophy in cases of decompensation. Just as in the treatment of cardiac decompensation we always insist on maintaining a high cardiac reserve, so in displacement we attempt to maintain a maximum pulmonary reserve. Collapse therapy, particularly of the conservative type, can take some of the load off the good lung and maintain that pulmonary reserve for such emergencies as pneumonia, cardiac decompensation, or some other conditions necessitating hyperventilation of the lungs.

The results of Hirakawa's (14) experimental work may be mentioned in support of our attitude of preserving pulmonary reserve. He performed a series of experiments on recently excised lungs of the mouse, and determined volumetric changes of the lungs under different internal air-pressures. He also determined the completeness of return to the original lung volume after removal of the pressure. The air-pressures were regulated by the elevation or lowering of a reservoir of mercury. Hirakawa noticed a slight initial resistance of the lung to the distending force. This resistance was diminished by the onset of fatigue in the preparation. Repetition of distentions caused the recovery of lung volume to its original state to become less and less complete. These experiments, having been on fresh specimens and checked with rubber balloons, tend to emphasize the tendency of the lung to an increased plasticity and a decreased elasticity.

In mediastinal displacement when the good lung is forced to expand in order to occupy the dead-space produced by the sclerosing lung, a certain degree of the normal reserve elasticity of the lung must of necessity be used up. We have been able by means of artificial pneumothorax to replace the mediastinum back to its normal position and thus maintain pulmonary reserve for emergencies, as mentioned above. We have used this procedure only in cases of pulmonary tuberculosis when collapse of

the lung was indicated. The mere displacement of the mediastinum *per se* is not regarded by us as an indication for collapse therapy.

This diminished elasticity may not be a great factor clinically, because the lung does not expand to its full volume under ordinary conditions. We know from experimental observations on fresh normal human lungs, which we obtained from the Cook County Hospital for study through the kindness of Dr. R. Jaffé and Dr. J. J. Kearns, that the lung can expand at least one-third more than the capacity of the chest-cavity. If, then, the room for the expansion is made by the sclerotic lung and since the chest-wall does not change materially to compensate for the diminished chest capacity on the pathological side, the usual result is to be expected. Nature abhors a vacuum and, with a mobile mediastinum and diaphragm, this space will be filled in accordingly. In the presence of a sclerotic lung on the better side or in the presence of a mediastinum that became immobile through inflammatory scarring, the diaphragm of necessity will rise and fill up the gap.

Experimental and clinical observations on the activity of the mediastinum have led us to assume that the mediastinum acts as a safety-valve for sudden changes of pressure in the thorax. Under normal conditions this structure is mobile and may get displaced to one or the other side of the thorax in order to equalize variations in volume or pressure on the two hemithoraces. Moreover, its layers are so arranged that there is a definite and easy access from the mediastinum to the outside. It is a common clinical experience to develop interstitial and mediastinal emphysema following sudden blows on the chest. In an experimental study of the aetiology of interstitial and mediastinal emphysema (15) an attempt was made to determine the cause of this condition. Our conclusions were that mediastinal and interstitial emphysema is apparently a protective mechanism on the part of the body to keep air from regions where it may cause difficulty. Anything that produces an increased intrapulmonic pressure, such as a severe cough, labor in childbirth, lifting of heavy objects, etc., probably causes a mild degree of mediastinal emphysema and air embolism. It has been possible for us to induce a marked mediastinal and interstitial emphysema in dogs *in vivo* by increasing the intrapulmonic air-pressure to a point over 60 mm. Hg. A few blasts often were enough to produce this emphysema. It is interesting to note that this emphysema, with its concomitant pneumothorax and air embolism, was in no way associated with any injury to the lung tissue.

We have observed that the pleura can easily be stripped from its adja-

cent lung if the intrapulmonic air-pressure is increased to a point between 60 to 100 mm. of mercury (16). Where the pleura strips off most readily is at the point of the reflections of the pleura at the hilum, where it ends as visceral and begins as parietal pleura. When an increase of intraälveolar pressure occurs, air finds its way through this site into the mediastinum. If the air is only of small amount, it remains there until it is absorbed. If there is a large amount of air-leakage, the emphysema may spread up toward the cervical fascial planes or downward through the *hiatus oesophageus* to the retroperitoneal tissues, and eventually find its way out through the inguinal rings.

The displacement of the mediastinal structures toward one or the other side also reinforces our attitude as to the safety-valve function of the mediastinum. Henry Sewall (35) cited quite a number of authors who have noticed motility of the mediastinum. Among them were Dumarest and Brette, Weil, Stivelman and Rosenblatt, Parfit, Pisoni, Rist, Hislop, Pearson, Hennell and Golembe, Packard, Oekonomopoulo, Barlow and Kramer, von Muralt, Emerson, and, as affecting children, Armand-Delille, Georges and Decrochet, and Babonneix and Denoyelle. Sewall's paper treats the literature on this subject so well that it would be needless duplication to discuss it further in this paper. To those who are interested in a critical review of this subject, we highly recommend Dr. Sewall's article. Knowing, then, that this phenomenon has been frequently observed, and realizing that there is a common misconception that pleuropulmonary adhesions are the basis of such a displacement, we shall try to analyze the fundamental principles involved in the displacement of the intrathoracic organs.

The thorax is a more or less rigid cavity, and the only parts in the chest that are displaceable to any appreciable extent are the diaphragm and the mediastinum. It is true that the ribs on the diseased side assume a position much closer to each other while those on the opposite side become more and more separated from each other. At best, however, this change is comparatively small when contrasted with the degree of change in the mediastinum or the diaphragm.

A. A. Freedman and H. H. Freilich, of our Dispensary staff, have been studying the relation of the interspaces to the underlying lung involvement and find that even long before any X-ray evidence occurs in the lung the overlying intercostal space just over it begins to shrink. They refer to this phenomenon as the Freedman-Freilich sign. These observations are limited primarily to the first and second interspaces. We have seen

this narrowing of intercostal spaces quite regularly in advanced unilateral tuberculosis, particularly in the fibroid type. There is a definite widening of the corresponding spaces on the opposite side.

In addition to changes in the chest-wall, we have noticed, also, a definite deviation in the normal contour of the spine. By taking X-ray plates of patients with unilateral tuberculosis in such a way so that the dome of the diaphragm as well as the pelvis were included in the picture, we noticed that, with the patient perfectly upright and the knees perfectly straight, the distance between the iliac spine and the costal margin was shorter on the diseased side. In addition to this shortening, it was evident that there was a slight but noticeable scoliosis of the spine with the convexity appearing on the good side.

The mediastinum, although supposedly a fixed tissue, is made up of loose areolar and fibrous tissue. It is attached to the spine on one side and the sternum on the other. It presents a definite motility associated with respiration. This motility is especially noticeable during fluoroscopic examination of pneumothorax patients with 90 to 95 per cent of lung collapse. This motility appears as a wave-like swaying toward the collapsed side coincidental with each inspiration. It should not be confused with the very slight degree of expansion of the lung, which is also noticeable during inspiration.

The vertebral attachment of the mediastinum is rather loose. One can easily peel off the whole mediastinum and its contents *in toto* by inserting the finger just behind the bronchi of a dog or a cadaver and peel off the tissues cephalad or caudad. As the lung contracts by virtue of fibrosis it leaves a potential dead-space. Only two organs can by necessity fill in this space. The diaphragm rises up from below and especially in cases in which the fibrosis is most extensive at the base. The mediastinum is the second organ or tissue that may shift over and, in so doing, force the good lung to expand slightly more and fill in the dead-spaces produced by the sclerosing lung.

The lung, being more or less of a passive organ and depending for its expansion primarily on the contractions of the diaphragm, the intercostal muscles, and the accessory muscles of respiration, has no ability to induce any pushing on the mediastinum. Being made up of a large amount of elastic tissue the lung has a tendency to contract. It expands, therefore, by virtue of the increased negative pressure induced by the diaphragm and the other muscles of respiration. It requires only 5 to 10 mm. of mercury to fully expand a lung in the presence of an open pneu-

mothorax, while the reserve power of the diaphragm measures up to 25 to 30 mm. Hg. We have been able to measure this reserve diaphragmatic strength by allowing compressed air to enter our own bronchial tree and measuring the pressure necessary to overcome the activity of the diaphragm.

In a microscopic study of the lung showing third dimensional views we (17) have observed that in fibrosis of the lung the interalveolar wall, which normally is so thin that one can see through it, becomes thicker, and in extreme grades of fibrosis the deposition of fibrous tissue is such that the alveolus has become completely obliterated by the thickened interalveolar walls. The respiratory function is now taken over by the bulbous portions of the terminal bronchioles which are less contractile. The natural sequence, therefore, is a contracture of the fibrous tissue and at the same time an additional amount of forcible expansion on the good lung. We know from experimental evidence on dogs and cadavers that the lung can be expanded at least one-third more than the total capacity of the chest-cavity. Given then an increased space in the chest-cavity and a mobile mediastinum, the good lung expands more and fills in the potential dead-space produced by the displaced mediastinum.

The only conditions in which it is possible for the mediastinum to be pushed over is that of new growth of the lung. Such a growth, when it becomes large enough to impinge upon the mediastinum, can and does press the mediastinum as well as the lung that it impinges upon. In such a case we have seen a definite rearrangement of the alveoli and bronchioles, so that they appear much like strands of tissue arranged adjacent to each other instead of the normal cuboidal contour.

The degree of displacement of the heart depends upon the degree of displacement of the mediastinum. We have often encountered X-ray plates of dextrocardia and the only designation of the proper anatomical position is the indicator on the roentgen film marking the right or left side. The opposite has also been true, and the right border of the mediastinum appeared well within the midportion of the vertebral bodies. Occasionally we have noticed distortions of the trachea much in the manner seen in enlargements of the thyroid gland. This type of distortion is seen particularly in cases with fibrosis and contracture of the lung limited to the apex.

Mediastinal displacement is evident also in cases of pleural effusions. In cases of acute effusions one often sees that the mediastinum is displaced toward the side opposite the effusion. This is true only in cases

in which the fluid has increased to such an amount that the intrapleural pressure is of necessity increased on the effusion side. A definite motility of the mediastinum is also evidenced in cases of hydropneumothorax. In a study of a series of our patients with hydropneumothorax we (18) have been able to notice that the mobility of the mediastinum is such that it may even cause an inspiratory rise of the fluid-level. On expiration the drop of the fluid-level does not seem to be so marked, but the inspiratory rise of this level is definite and may vary from 1 to 5 cm. Coincident with this rise, we have also noticed a deviation of the mediastinum toward the pneumothorax side and a subsequent return to its normal position with expiration. This phenomenon has led us to presuppose that pleural effusions might in some way disturb the normal tonus of the diaphragm so that it would act as in Kienboeck's paradoxical inspiratory rise of the diaphragm. Such an assumption may be obvious, because in the majority of effusions the diaphragm cannot be seen either in the film or with the fluorescent screen. Our difficulty has been cleared up by a fortunate coincidence in two cases of hydropneumothorax in which there was a very small amount of lung tissue intervening between the dome of the diaphragm and the base of the fluid. In both these cases we noticed normal inspiratory fall and expiratory rise of the diaphragm. One must conclude, therefore, that the mediastinum is responsible for this rise because the diaphragmatic fall at inspiration would of necessity tend to cause a drop in the fluid-level. This rise would then represent the difference in displacement between the diaphragm and the mediastinum.

Our findings confirm those of Maestrini (22), who finds a similar inspiratory displacement of the mediastinum toward the pneumothorax side coincident with the inspiratory rise of the fluid-level. In his case Maestrini found that the diaphragm played no rôle in this rise of fluid-level. We have noticed abnormal diaphragmatic motility only in two types of phenomena. The first is the result of paralysis of the diaphragm from a phrenic neurectomy or injury to the nerve. The second condition is noticed during the act of eructation, when we (19) find an independent but coincidental activity of the two hemidiaphragms. Here we noticed that there is a series of repeated rapid contractions of the left diaphragm with coincidently repeated relaxations of the right diaphragm. These movements of the diaphragm bring about a decrease in the acuteness of the angle at the cardia and aid in the expulsion of air from the fundus of the stomach.

Our findings on mediastinal displacement are somewhat at variance with

those of Lilienthal and his associates (21). Their findings can be briefly summarized as follows:

1: In open pneumothorax or pleurisy with effusion:
a. Expiration or cough results in a gush of pus or ejection of air.
b. Inspiration causes air to rush into the chest.
2: Fluorescent-screen examination of the lung (open pneumothorax):
a. Forced expiration causes lung expansion on the thoracotomy side.
b. Inspiration causes a decrease in lung volume on the thoracotomy side.
3: Fluorescent-screen examination of the mediastinum (open pneumothorax; mobile mediastinum):
a. Expiration leads to deviation of the mediastinum toward the thoracotomy side.
b. Inspiration will cause a flop of the mediastinum toward the normal side.
4: Fluorescent-screen examination (closed pneumothorax; no bronchial fistula):
a. Inspiration or straining with closed glottis results in an immobile mediastinum.
b. Expiration causes a displacement toward the normal side (opposite of *3*).
c. Expiration causes a decrease in the lung volume (opposite of *3*).

This study of mediastinal displacement by Lilienthal and his associates emphasizes the presence of such a displacement under varying conditions. The safety-valve function of the mediastinum is also touched upon in this report. Lilienthal attributes a prognostic value in this mobility and states that, in cases of empyema, the greater the motion of the mediastinum, the better the chance of curing the patient of the empyema. We agree with the authors on the prognostic value of this mobility, which may also be applied to conditions other than empyema. We noticed a somewhat different displacement of the mediastinum in our cases of artificial pneumothorax. We invariably noticed an inspiratory deviation of the mediastinum toward the pneumothorax side and a return to a resting position at expiration. This variance of our findings from those of Lilienthal is probably the result of differences in the intrapleural pressures of our patients. Very seldom do we allow the intrapleural pressure to be higher than -2 cm. of water at the end of a pneumothorax treatment. We prefer to keep these end-pressures at -6 to -8 cm. of water, and our treatments are guided primarily by the degree of intrapleural pressure rather than by the amount of air injected. We would much rather give 100 to 200 cc. of air and keep the intrapleural pressure lower than give more air at the expense of placing the cardiocirculatory reserve

under a strain. This routine necessitates more frequent treatments, but these are borne more easily by the patients than the resulting tight feeling and dyspnoea which may be experienced with the maintenance of higher end-pressures in the pleural cavity.

A yielding mediastinum is sometimes a source of difficulty during the course of pneumothorax collapse. There are instances when prompt collapse of the lung may save the patient's life. Such is often the case in pulmonary haemorrhage. In such instances we are sometimes forced to inject large amounts of air in a very short time, and frequently we have to increase the intrapleural pressure to a high level. No difficulty may arise if the mediastinum is fixed and the increased intrapleural pressure does not tend to be equalized by a mediastinal displacement toward the side of lesser intrapleural pressure. More commonly, in cases of acute collapse, we are apt to find such a shift, and in a good many of these cases a mediastinal hernia is likely to result. This appears on the roentgen film as an area of lessened density just behind the aortic arch. Nitsch (28) was among the earliest workers to demonstrate the possibility of mediastinal displacement. He reported two weak places in the mediastinum, the first being just under the manubrium, and the second being in the lower posterior portion of the thorax at a point where the parietal pleura walls in a potential place, bounded behind by the spine and the descending aorta and in front by the oesophagus and the heart. It is at this point where Grocco's sign is elicited when displacement takes place as a result of fluid present in the chest-cavity.

At times even manometric readings cannot tell the true state of affairs. In cases in which the mediastinum "gives" easily even under only slightly increased intrathoracic pressures, a large amount may be easily introduced into the pleura, to the point of causing displacement of the mediastinum, but still with the intrapleural pressure remaining comparatively low. This is particularly true in younger individuals and especially those that show little or no tracheobronchial lymph-node involvement. Sorgo (37) considers this excessive shifting of the mediastinum as a complication and proposes a means of avoiding it. Instead of injecting air with the usual pneumothorax apparatus, he proposes the introduction of air into the pleural cavity by the simple aspiration of filtered air. We feel that such a procedure in pneumothorax collapse is really a step backward, because there is no way of determining exactly what happens in the chest during the injection. Sorgo proposes this treatment especially in patients with a sensitive circulatory system. It is true that excessive intrapleural

pressures may produce undesirable circulatory changes. It is for this reason that in our routine at the pneumothorax clinic we insist on frequent small injections rather than larger amounts given at longer intervals. We agree with H. Alexander (2) who warns against unnecessary pressure increase in pneumothorax, and cites a case in which, shortly after pneumothorax had been made, repeated haemorrhages occurred. In order to effect compression of the bleeding vessel the pressure was more and more increased, but it was overlooked that a yielding mediastinum existed and that the haemorrhages were the result of stasis. The haemorrhages ceased at once when the opposite measures were taken; that is, after the pneumothorax had been reduced so that the mediastinum was in a normal position and its pendular movements were limited to a minimum.

Alexander's experience conforms with ours in a case of pulmonary haemorrhage.

A male patient, J. S., 25 years old, had a severe haemorrhage. The Pneumothorax Clinic was notified and one of its consultants was promptly dispatched to this man's home. The doctor spent two hours with this patient, and 1,000 cc. of air were injected at two sittings. The second injection was made because the patient persistently kept raising large amounts of fresh blood. Sedatives were given, and other conservative measures were instituted, but the patient kept raising fresh blood, though now in lesser amounts. A portable X-ray apparatus was not available at the time, so that it was difficult to determine exactly what was happening in the pleural cavity. The intrapleural pressure was never raised any higher than +8 cm. of water. The patient bled persistently in spite of repeated injections of air into the chest, so that in four days' time the patient received 3,500 cc. of air. Because of marked acute haemorrhage a blood transfusion was considered necessary, and the patient was removed to the Columbus Hospital of Chicago, where the transfusion was made. An X-ray of the chest was taken by Dr. H. E. Davis on admission and a definite mediastinal hernia was noticed. Air, therefore, was aspirated from the chest until the severe dyspnoea was relieved. Another X-ray taken after this procedure showed no mediastinal hernia. As a result of this aspiration and the relief of the herniation, the haemorrhage stopped and did not recur. Pneumothorax collapse was maintained, but only a 75 per cent collapse was maintained, with the intrapleural pressures remaining at a point of −5 to −8 cm. of water. With these end-pressures, cyanosis or dyspnoea was no longer present, and the patient was very comfortable.

Mediastinal displacement, with or without diaphragmatic rise, can also be noticed in acute conditions, such as pneumonia or massive atelectasis of

the lung. Cases of such displacement have been reported by Wu (43). Out of 40 consecutive cases of lobar pneumonia in human subjects, mostly adults, five showed displacement of the heart and trachea to the affected side and 22 showed an elevation of the diaphragm on the affected side. In 105 cases of experimental pneumonia in dogs there were 42 instances of visceral displacement. Among others who reported such displacements, Wu cites Thoenes (39), Wallgren (41), Griffith (10), Hart (11), and Terrell and Robertson (38). The mechanism involved in these acute cases is no different than that present in chronic sclerosis. Nature abhors a dead-space, and in the presence of any condition in which an imbalance in pressures or volumes results in the two hemithoraces an equilibrium is obtained either by a mediastinal shifting or, in cases of a relatively immobile mediastinum, by a proportionate rise of the diaphragm on the affected side and a proportionate collapse of the chest-wall.

Diaphragmatic rise is a passive condition of the diaphragm. The less the tonus of the diaphragm the higher it may rise. This rise of the diaphragm depends upon a normal or increased activity of the contralateral hemidiaphragm. In a roentgenological study of a series of cases with phrenic neurectomy we (46) have noticed that the degree of diaphragmatic rise depended, among other things, upon the degree of tonus of the diaphragm on the opposite side. Thus, a woman who breathes primarily with her ribs may not get as good a diaphragmatic rise as a muscular male who breathes through the activity of his diaphragm. When the normal contraction impulses are cut off by the phrenic neurectomy and, as a result, also atrophy of the muscle ensues, the tendency of the diaphragm is to rise. Moreover, the rigid chest-wall, with the negative intrathoracic pressure and the persistently rising intraäbdominal pressure upon coughing, lifting of heavy objects and other activities necessitating a contraction of the abdominal muscles, generally aids in pushing the atonic hemidiaphragm upward. In cases in which the tonus of the diaphragm remains equally balanced on both sides and there is a diminished lung volume from a chronic or an acute lesion the degree of rise would depend entirely upon the degree of mobility of the mediastinum and the extent of pulmonary contracture. Brown (3) has made an interesting X-ray observation worth noting. He noticed that when the elevation is due to intraäbominal pressure, phrenic paralysis, atelectasis or enlarged liver, the diaphragm is found elevated on the affected side, but the relation in the relative heights of the anterior or posterior attachments of the diaphragm remains the same. In case of subphrenic abscess he found that

the posterior portion is elevated and is at times even higher than the anterior portion. The posterior costophrenic angle is usually obliterated, and the tissues above it show evidence of inflammatory changes. This observation is important, not only because it relates to different portions of a hemidiaphragm but also because it offers a very good diagnostic sign in cases of subphrenic abscess.

SUMMARY AND CONCLUSIONS

1. Dextrocardia should be studied to determine whether it is a true dextrocardia with or without heterotaxia.

2. Acquired dextrocardia depends upon pulmonary pathological changes which cause displacement of the mediastinum.

3. Only those in whom there is a cardiac displacement to such an extent that the whole heart lies to the right of the left sternal border should be considered as cases of acquired dextrocardia (Hedblom).

4. Mediastinal displacement does not presuppose the presence of pleuropulmonary adhesions and it should not be considered as a contraindication for pneumothorax collapse.

5. If there is a definite indication in the lungs for collapse therapy, mediastinal displacement may be corrected by means of artificial pneumothorax, and thus the pulmonary reserve of the good lung may be preserved for any emergency disease that may require hyperventilation of the lungs.

6. The mediastinum may be regarded as a safety-valve, used for equalizing variations in pressures and volumes in the two hemithoraces. Nature abhors a vacuum or a dead-space, and in the chest it utilizes the mediastinum or the diaphragm or both to bring about a normal balance whenever the occasion arises.

7. The chest-wall also retracts to a lesser extent on the affected side in an attempt to balance differences in pressures and volumes in the two hemithoraces (Freedman-Freilich sign).

8. The main condition in which the mediastinum may actually be pushed is in the case of mediastinal or pulmonary neoplasm.

9. In cases of hydropneumothorax an inspiratory mediastinal displacement toward the affected side may cause a rise of the fluid level from 1 to 5 cm. The diaphragm reacts normally in these cases, and the degree of elevation represents the difference between the inspiratory contraction of the diaphragm and the inspiratory shift of the mediastinum toward the affected side plus a very slight pulmonary expansion.

10. We believe that variation of mediastinal displacement with inspiration and expiration depends upon the intrapleural pressure at the time of the examination. If the intrapleural pressures are high we would expect an immobile mediastinum at inspiration. If the intrapleural pressures are low, we may expect a shift toward the affected side.

11. Mediastinal mobility may be used as a prognostic sign in empyema. The greater the motion of the mediastinum in empyema, the better the chance of curing the patient (Lilienthal).

12. A yielding mediastinum may sometimes cause confusion, in that with apparently low intrathoracic pressures excessive displacement of the mediastinum or even mediastinal hernia may result during artificial pneumothorax. X-ray studies of such patients will prevent such a difficulty.

13. Mediastinal displacement may occur in chronic as well as acute conditions that cause an imbalance of volumes or pressures between the two hemithoraces. Among the acute conditions, lobar pneumonia and massive atelectasis of the lung are the commonest. Any chronic condition that causes a unilateral pulmonary sclerosis will result in a mediastinal shift or a diaphragmatic rise.

14. The diaphragmatic rise of an otherwise normal hemidiaphragm is also a compensatory measure to balance differences in volume. This rise is more likely to be noticed when there is a decreased mobility of the mediastinum.

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THE BEHAVIOR OF PLEURAL EFFUSION IN HYDROPNEUMOTHORAX[1]

MINAS JOANNIDES

Pleural effusions are common in tuberculosis patients who are receiving pneumothorax treatments. The aetiological factors of effusion may be either infectious, mechanical or chemical. Infection may be introduced from the air that is injected into the pleural cavity, and, more frequently, through improper manipulation of the point of injection, or imperfect technique in the insertion of the needle. In spite of mechanical and chemical sterilization of the skin, and, in spite of the fact that the needle may be properly boiled or sterilized by means of chemical agents, infections may be introduced into the pleural cavity if the needle is inserted improperly into the chest. It has been customary for physicians who do thoracentesis to localize with the tip of their finger the intercostal space at the point of insertion of the needle. This, of course, is quite the proper technique if the physician used perfectly sterilized gloves and also strict operating-room technique. The usual experience, however, is that such needle insertions are made without the use of gloves, and, in spite of careful chemical and mechanical cleansing of the hands, pathogenic bacteria are bound to remain at the tips of the fingers. The bacteria are implanted on the skin of the patient and may be introduced along with the needle into the pleural cavity, thus causing infection. To prevent this source of infection it has been customary at the Pneumothorax Clinic of the Chicago Municipal Tuberculosis Sanitarium to insert the needle into the subcutaneous tissue first, and then localize the intercostal space at a point slightly above the site of the skin insertion of the needle, so that neither the skin nor the needle may come in contact with the operator's hand. This procedure, I am sure, has helped us to minimize the cases of pleural effusion in the Pneumothorax Clinic. Out of 5,610 pneumothorax injections we have had only 27 cases of pleural effusion, 10 of which developed on the right and 17 on the left side.

There is also an endogenous source of infection. Experimental work

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in the Research Laboratories of the Municipal Tuberculosis Sanitarium and clinical evidence at the Pneumothorax Clinic have convinced us that an infection in the periphery of the lung finds its way by continguity and

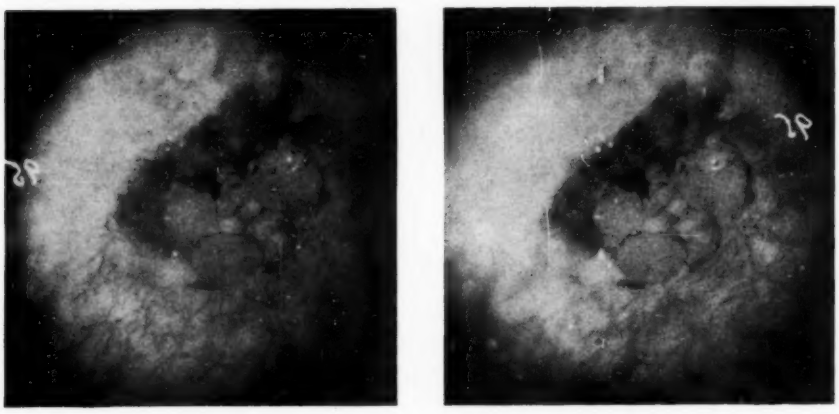

FIG. 1. Stereomicrophotograph, showing a group of tubercles on the pleural surface of the lung. To obtain a good third dimensional view get proper focal distance with a stereoscope and keep looking until depth shows up. Reproduced from the *Atlas of Surface Stereomicroscopy of the Lung*, Keystone View Company, Meadville, Pennsylvania, publishers.

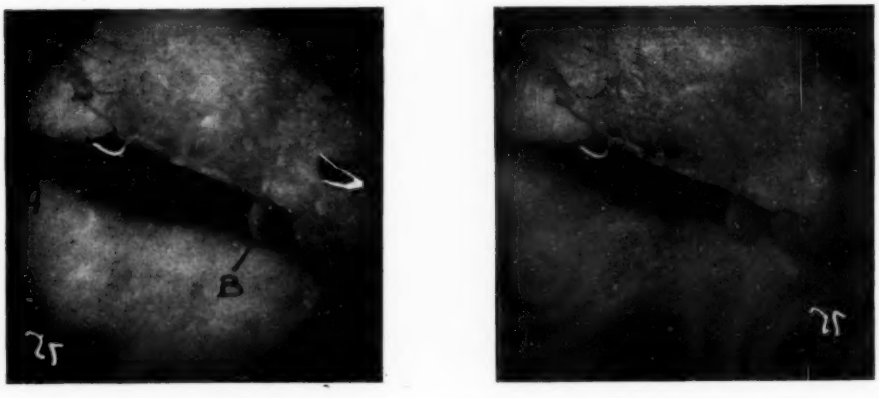

FIG. 2. Tip of lung, showing tubercles *A* and *B*, one of which is in the process of separating and the other hanging by a blood-vessel pedicle. Reproduced from the *Atlas of Surface Stereomicroscopy of the Lung*, Keystone View Company, Meadville, Pennsylvania, publishers.

extension to the pleura and produces a localized pleurisy. (Minas Joannides: *The Protective Power of the Pleura*, *Am. J. M. Sc.*, clxxx, 833: December, 1930). In such a case the pleural cells have a tendency to

produce adhesions from an inflammatory reaction on the surface of the pleura. Fibrinous adhesions occur as a result of this inflammation and, in the course of a pneumothorax treatment, these may rupture. By coming in contact with the atmospheric air that is present in the pleural cavity, the injured surface of the pleura is exposed to the atmospheric air, and, if the air is contaminated, it may produce exudative pleurisy. If the adhesions are fairly dense, so that rupture of the adhesions follows in the presence of artificial pneumothorax, it may result in a fairly large tear of the lung (thus mechanically doing away with the hydrostatic protective power of the pleura). The lung tissue-juices then may begin to exude from the lung into the pleural cavity. These, of course, being in contact with infected material from the bronchial tree, and, in the presence of atmospheric air which is introduced with the artificial pneumothorax, may lead to beginning irritation of the pleura, so that massive pleural effusion may occur. Such a condition would be analogous to acute general peritonitis following a perforation of any intraäbdominal viscus.

Another aetiological factor which is not frequently recognized is implantation tuberculosis of the pleura which results in pleurisy with effusion. In a surface stereomicroscopic study of the lungs from a large number of specimens studied in the *Pathologische Abteilung of the Reichsarbeits Ministerium*, Berlin, Germany, through the kindness of Professor Max Busch, the Director of this museum, we have been able to find tubercles on the external surface of the lung, which had ordinarily gone unnoticed because of their small size, thereby making them invisible to the naked eye (see figure 1). In one particular specimen, especially (see figure 2) we noticed a tubercle located at the tip of the lung well separated from the surface of the lung tissue and hanging free in the pleural cavity, being held only by a blood-vessel pedicle. Such a tubercle, when dislodged and falling into the pleural cavity, is bound to cause a tuberculous pleurisy. When this tubercle breaks down, a large number of tubercle bacilli are liberated in the pleural cavity and are likely to cause tuberculous pleurisy with effusion. We believe that this is one of the main causes of silent pleurisy with effusion associated with pulmonary tuberculosis.

Among the chemical causes of pleural effusions one must not forget the reaction of oxygen, carbon dioxide, and nitrogen, which act as irritants to the endothelium of the pleura, thereby causing a definite degree of inflammatory reaction, which, if massive enough, may lead to effusion. Other chemicals which are commonly used at present are various types of oils which are being utilized in the induction of oleothorax for collapse

therapy. In an experimental study on dogs (Minas Joannides and E. H. Seabright: *Oleothorax, an Experimental Study of the Pleural Reactions to Various Types of Oils*, to be published), we have found that the oils commonly used for the induction and maintenance of oleothorax act as irritants to the pleural surface, thereby inducing a peanut-butter type of pleurisy with effusion. Oil removed from such experimental animals, on standing, forms into layers. The lowermost is made up of tissue cells and pus, the second layer of serous or bloody incoaguable fluid, while the topmost layer is of unchanged oil. Our experience with cases of pleural effusion seen in the Pneumothorax Clinic has been that the majority of the patients complain of severe pain immediately after the injection of air and that they may or may not have a chill. This pain subsides in 24 to 48 hours, and invariably such a patient when seen within 48 hours shows fluid if examined by X-ray. In such cases the amount of fluid is so small that it cannot be recognized by physical signs, but can be readily seen in fluoroscopic examination, or by obtaining an X-ray film. Our feeling is that these cases have pleuropulmonary adhesions, which undoubtedly are being stretched because of the pneumothorax, and eventually break, thus causing either an exposure of a small portion of the lung, or a tear of the parietal pleura, which may result in a pleural effusion.

Patients with hydropneumothorax do not show any special clinical picture unless the pleural effusion becomes infected. Such an infection may lead to a rise of temperature and other signs of pyogenic infection. It has been customary at our Pneumothorax Clinic to aspirate a small amount of fluid, varying from 100 to 500 cc. at each time, and to replace this fluid with air.

In our study of these patients we have observed a phenomenon not hitherto described. We have found that the fluid-level varies with normal respiratory movements of the diaphragm. In following up such cases with the fluorescent screen, we have found that there is an inspiratory rise of the fluid-level and expiratory fall of this level. This variation in the level of the fluid may range from 1 to 5 cm., depending entirely upon the tonus of the diaphragm on the good side. At the outset one would think that this is contrary to ordinary reasoning because we would expect an inspiratory fall of the fluid-level and an expiratory rise of this level. One would assume that such would be the case, because we know that the diaphragm under normal conditions goes down with inspiration and up with expiration. One would conclude, therefore, that in cases of effusion something may happen to the

diaphragm so as to cause an inspiratory rise of the diaphragm. That would be the logical assumption, because in most cases of pleural effusion the outline of the diaphragm is not definitely visible, and it is difficult to determine the exact activity of the diaphragm on the hydropneumothorax side. We might think of this phenomenon as another instance of an independent activity of the two hemidiaphragms. We know that such is the case in the development of eructation (Minas Joannides: *Mechanics of Eructation, Jour. Thoracic Surg.;* in press), since we have studied the diaphragm and have seen that there is an independent and opposite movement of each hemidiaphragm. In eructation we have noticed that there is a series of repeated rapid contractions of the left diaphragm with coincidently repeated relaxation of the right hemidiaphragm. A careful study of all of our cases of pleural effusion has definitely disproved the assumption of the presence of any pathological activity in the diaphragm.

Two cases in which there is a small amount of lung tissue present between the diaphragm and the base of the fluid have helped us to get at the exact mechanics of this phenomenon. In both of these cases we have found that the diaphragm contracts downward with each inspiration, regardless of the amount of fluid present in the pleural cavity. We have also noticed that the fluid-level rises with each inspiration in spite of the normal descent of the diaphragm on the hydropneumothorax side. Fluoroscopic observation on the activity of the mediastinum has definitely shown us that the mediastinum is displaced from 1 to 4 cm. toward the pneumothorax side with each inspiration. Such a displacement becomes more evident especially when the intrapleural pressure on the pneumothorax side is diminished to from − 10 up to − 18 cm. of water. When the intrapleural pressure is diminished there is a small degree of expansion of the lung tissue itself, and this aids in the production of a further rise of the fluid-level in effusion. Mediastinal displacement is a very common phenomenon and has been studied very carefully by a large number of phthisiologists. Henry Sewall (*A Critique of Artificial Pneumothorax in Pulmonary Tuberculosis, Amer. Rev. Tuberc.*, xviii, 118) made an extensive study of this problem and has shown that the mediastinum is a mobile structure. In our study of 250 consecutive cases (Minas Joannides: *Displacement of Intrathoracic Viscera Resulting from Pathological Processes in the Lung, Amer. Rev. Tuberc.*, 1934, xxix, 313) we became convinced that the mediastinum acts as a safety valve to equalize variations in pressure between the two sides, and also variations

in volume between the two sides. We have also found that a mediastinal displacement does not necessarily occur only in cases of pneumothorax, but may occur in any case of underlying lung involvement which would tend to decrease the volume of the lung tissue. The mediastinum, as a result of diminished lung volume on the diseased side, would have a tendency to shift toward the sclerotic side, and in this way aid in the obliteration of the potential dead-space produced by the sclerotic lung. We have also found that the diaphragm on the diseased side may also show a tendency to rise. This rise depends upon two factors, namely, on the degree of mobility of the mediastinum, and also the decrease in the tonus of the ipsolateral hemidiaphragm.

CONCLUSIONS

Pleurisy with effusion is quite a common sequel in collapse therapy by artificial pneumothorax. It is not dangerous in itself unless secondary infection is introduced or effusion results from an infection introduced either through the lung or from the outside. The number of cases with pleural effusions may be diminished by a careful and rigid observance of the rules of asepsis during the insertion of the needle and by the injection of uncomtaminated air into the pleural cavity. We feel it advisable to aspirate definite amounts of fluid and introduce air in order to maintain a hydropneumothorax, so that, if at any time the effusion becomes rapidly absorbed, it will prevent the formation of pleuropulmonary symphyses. An inspiratory mediastinal displacement is noticed in cases of hydropneumothorax, and this mediastinal displacement is toward the pneumothorax side, thus causing a rise in the fluid-level. We are certain that this rise has nothing to do with any pathological activity of the diaphragm on the hydropneumothorax side. Our study of the subject has led us to assume that the tonus of the ipsolateral hemidiaphragm remains intact regardless of the amount of fluid present in the chest.

Note: Besides the several studies cited in the foregoing text, the reader is referred to: Minas Joannides: *An atlas of surface stereomicroscopy of the lung.* Published by the Keystone View Company, Meadville, Pennsylvania.

BLOOD-PRESSURE VARIATIONS IN TUBERCULOSIS

A Statistical Study of the Range of Arterial Tension

EMIL BUNTA[1]

INTRODUCTION

A review of medical literature shows that blood-pressure studies relating to tuberculous and nontuberculous diseases have, almost without exception, been predicated on simple mathematical averages. In view of existing statistical methods of analysis and interpretation the use of such averages is inadequate because they do not provide for normal deviation, nor define the range of normal and abnormal tension. Some light has been shed on this subject in an article by Faber and James (1) dealing with the range and distribution of blood-pressure in normal children. The rationale of blood-pressure range from a clinical standpoint is embodied in that contribution.

The object of the present study was to determine the range of arterial tension in tuberculosis.

TECHNIQUE

This investigation was conducted at the South Side Dispensary, one of the Municipal Tuberculosis Sanitarium dispensaries located in Chicago. There is an annual turnover of 37,000 patients in this clinic, including 6,500 officially registered cases, of which 2,000 are tuberculous, and the remainder under observation. From the multiplicity and variety of nontuberculous individuals examined, suitable norms were selected for research purposes. The tuberculous patients studied were taken at random in the course of dispensary routine.

Individual records were kept on cards bearing the name, age, sex, height, weight, pulse-rate, systolic-, diastolic- and pulse-pressure readings and clinical diagnosis.

The pulse, height and weight measurements were obtained by the clinic nurse. All physical and blood-pressure examinations were made by the author. Each patient was tested in a sitting position, with the left arm

[1] Chicago, Illinois.

resting, relaxed and semiflexed, on the examiner's desk. A short preliminary rest was allowed to put the subject at ease.

Sphygmomanometric measurements were made with an anaeroid instrument, calibrated to 300 mm. Hg and provided with an adjustable dial. The auscultatory method was used, the systolic pressure being taken at the point of the first clear sound, and the diastolic at the beginning of the fourth phase. A relative check-up of this instrument was made with the aid of a standard mercury manometer.

STATISTICAL METHOD

In computing the blood-pressure data the "method of frequency distribution" of Pearson was employed, which permits the determination of the mean or average pressure, and the standard deviation or deviation from the average. The standard deviation is obtained by subtracting each member of the series from the mean, squaring these differences, finding the arithmetical mean of these squares, and extracting the square-root. This method, especially applicable to variables, takes into account the modal or most frequent value, and dispersion or scattering of values among all members of the series. If the distribution of such a series were plotted a curve is obtained known as the "frequency polygon."

Systolic-, diastolic- and pulse-pressure readings were tabulated by frequency distribution, using class intervals of 5 mm. Hg, and the mean and standard deviation computed from each distribution. The standard deviation, designated by plus and minus values indicating deviations above or below the average, defines the normal range, that is, the minimum and maximum limits of normal pressures.

The deviation index was utilized in estimating the various clinical levels or range of arterial tension. This index is obtained by finding the difference between the actual reading and the average finding according to age, sex, and weight, and dividing the result by the standard deviation. The deviation index, signified in terms of plus and minus values indicating deviations above or below the average, defines the boundaries of five pressure levels: namely, the range of absolute normal pressures; the range of relative hypotension and hypertension; and the range of absolute hypotension and hypertension. Deviations of less than 1 determine the range of absolute normal pressures. Deviations of 3 fix the inner limits of absolute abnormal low and high pressures, that is, the range of absolute hypotension and hypertension. Deviations varying between 1 and 3 mark off the intermediate or doubtful zones corresponding with the

range of relative hypotension and hypertension. Pressures falling within the latter zones belong to either normal or pathological cases, the exact nature of which is ascertained by other diagnostic measures.

CLASSIFICATION OF PATIENTS

The subjects of this study were classified according to clinical diagnosis into two major divisions, the normal and tuberculous cases. A total of 3,411 blood-pressure determinations were made on 2,915 patients. The distribution of these readings is shown in table 1.

Tuberculous patients were arranged into three groups. The first consisted of 955 pulmonary tuberculous individuals, free from signs of cardiorenal disease, on whom a total of 1,356 blood-pressure readings were made. The second group, including 221 pulmonary tuberculous patients with cardiorenal complications, had a total of 312 readings.

TABLE 1

Distribution of blood-pressure readings according to major clinical groups

CLINICAL GROUPS	TOTAL NUMBER OF PATIENTS	TOTAL NUMBER OF BLOOD-PRESSURE DETERMINATIONS
Normal	1,671	1,671
Tuberculous	1,244	1,740

The last group, made up of 68 lymphatic and bone tuberculosis cases, had a total of 72 blood-pressure measurements.

The pulmonary cases uncomplicated by cardiorenal lesions were subdivided according to pathological and clinical stages, following the classification of the National Tuberculosis Association (2).

All normal and tuberculous patients were classified by sex according to age and weight. Three age-groups were selected: the first included those under the age of 20; the second those between the ages of 20 and 39, inclusive; and the third, those 40 years of age or over. Three weight divisions were used, the normal, underweight and overweight. The normal group included those weighing within 5 per cent above or below normal weight standards. Individuals varying 5 per cent or more over normal weight made up the overweight group; while those who were 5 per cent or more substandard comprised the underweight group. The normal weight standards for children under the age of 15 were taken from the tables of heights and weights of children as prepared by Prof. Bird T.

Baldwin and Dr. Thomas D. Wood. Norms for patients 15 years or over were selected from the Grays' table (3).

NORMAL BLOOD-PRESSURE VARIATIONS

A total of 1,671 nontuberculous individuals, free from signs of cardiovascular or nephritic disease, served as controls for the tuberculosis cases. Negro and white patients were equally represented in the control group. Females slightly outnumbered the males. Of the total, one-third were children under 15 years of age. The average age of norms

TABLE 2

Mean pressures and standard deviations in mm. Hg for males in control group

NUMBER OF CASES	WEIGHT GROUP	PRESSURE LEVELS	UNDER 20		20–39		40 AND OVER		TOTAL AVERAGE	
			Mean	S.D.*	Mean	S.D.	Mean	S.D.	Mean	S.D.
310	Underweight	Systolic	102	7.7	122	8.0	122	13.3	122	9.9
		Diastolic	62	6.6	82	9.1	82	9.4	82	8.0
		Pulse-pressure	42	4.7	42	8.3	42	9.4	42	5.9
322	Normal weight	Systolic	102	7.7	122	9.4	122	10.4	122	9.4
		Diastolic	62	7.0	82	9.8	82	5.8	82	8.0
		Pulse-pressure	42	5.2	42	6.2	42	8.1	42	5.5
192	Overweight	Systolic	102	11.2	122	11.0	127	7.3	122	10.8
		Diastolic	62	8.0	82	6.8	82	6.8	82	7.2
		Pulse-pressure	42	5.6	42	7.5	42	9.6	42	4.9
824	Total average for all weight groups	Systolic	102	6.0	122	4.8	122	9.1	122	6.4
		Diastolic	62	4.5	82	5.5	82	6.9	82	4.7
		Pulse-pressure	42	3.7	42	4.9	42	7.1	42	4.2

* Standard deviation.

was 23.2 years; average height, 62 to 66 inches; average weight 111 to 143 pounds; and average pulse-rate 81 to 93.

Systolic measurements of the normal patients as a group varied from a minimum of 70 mm. to a maximum of 154 mm. mercury. The mean pressure was 112 mm. and standard deviation 5.3 mm., representing a normal systolic range of 107 to 117 mm. mercury.

Diastolic readings varied from 40 mm. to 100 mm. mercury. The mean pressure was 72 mm. and standard deviation 3.1 mm., defining a normal diastolic pressure range of 69 to 75 mm. mercury.

Pulse-pressures varied from 20 to 70 mm., the average being 42 mm.

with a deviation of 3.0 mm. Normal pulse-pressure, therefore, ranged from 39 to 45 mm. mercury.

Average pressures with corresponding standard deviations for both sexes in the control group, classified according to age and weight, are shown in tables 2 and 3.

Identical pressures were noted in children of both sexes under the age of 20. Pressure levels, both systolic and diastolic, were lower in childhood than in adult life. Between the years of 20 and 39, systolic and diastolic pressures of women averaged 10 mm. less than those of men.

TABLE 3

Mean pressures and standard deviations in mm. Hg for females in control group

NUMBER OF CASES	WEIGHT GROUP	PRESSURE LEVELS	UNDER 20		20–39		40 AND OVER		TOTAL AVERAGE	
			Mean	S.D.*	Mean	S.D.	Mean	S.D.	Mean	S.D.
394	Underweight	Systolic	102	8.0	112	10.0	127	10.9	112	8.6
		Diastolic	62	6.5	72	8.6	82	14.1	62	6.8
		Pulse-pressure	42	5.7	42	5.6	42	10.4	42	4.2
235	Normal weight	Systolic	102	11.2	112	8.7	132	16.0	112	13.3
		Diastolic	62	7.3	72	8.9	64	5.7	72	7.7
		Pulse-pressure	42	7.6	42	8.6	52	10.9	42	6.7
218	Overweight	Systolic	102	12.6	112	8.5	132	17.3	112	13.0
		Diastolic	62	9.1	72	9.3	82	13.6	72	8.2
		Pulse-pressure	42	8.6	42	5.0	42	6.2	42	5.8
847	Total average for all weight groups	Systolic	102	6.4	112	6.8	132	10.3	112	7.7
		Diastolic	62	4.2	72	5.8	82	8.7	72	4.5
		Pulse-pressure	42	4.0	42	3.7	42	9.7	42	3.5

* Standard deviation.

After the age of 40, systolic pressures of women averaged 10 mm. higher than men. Diastolic and pulse-pressure variations were also greater in female patients.

Weight influenced blood-pressure in lesser degree than sex or age. Mean pressures for either sex were similar in all weight divisions. Overweight males showed slightly greater systolic variability; and males in the normal weight and underweight groups revealed somewhat larger diastolic and pulse-pressure deviations. Females, on the other hand, exhibited relatively wider variations at all pressure levels in both normal weight and overweight classes.

The range of arterial tension in normal patients as defined by the deviation index is shown in table 4. Pulse-pressures showed the highest and systolic readings the lowest incidence of absolute normal pressures. Systolic pressures occurring outside normal limits predominated in the range of relative hypertension. Diastolic and pulse-pressure deviations were directed primarily toward relative hypotension levels. Less than 1 per cent of all readings for each component of arterial tension reached abnormal limits. In view of these observations, pulse-pressures exhibited the least, and systolic pressures the greatest normal variability. In other words, systolic pressures manifested the greatest instability, and pulse-pressures the utmost stability under normal conditions.

TABLE 4

Blood-pressure range in normal patients as defined by the deviation index

BLOOD-PRESSURE RANGE	DEVIATION INDEX	SYSTOLIC		DIASTOLIC		PULSE-PRESSURE	
		Cases	Per cent	Cases	Per cent	Cases	Per cent
Absolute hypertension	+3 over	11	0.6	0	0	3	0.1
Relative hypertension	+1 to +3	327	19.6	275	16.5	210	12.6
Normal	+1 to −1	1,029	61.6	1,074	64.3	1,176	70.4
Relative hypotension	−1 to −3	301	18.0	316	18.9	269	16.1
Absolute hypotension	−3 under	3	0.2	6	0.3	13	0.8
Total		1,671	100	1,671	100	1,671	100

BLOOD-PRESSURE VARIATIONS IN TUBERCULOUS PATIENTS

Of the 1,244 patients comprising the tuberculosis group, 56 per cent were Negroes. Males were slightly in the majority. One-fifth of all tuberculosis patients were children under 20 years of age. Individual ages varied from 3 to 82 years, the average for the group being 27.0 years. Their height averaged from 60 to 68 inches; weight from 102 to 142 pounds, and pulse-rate from 87 to 108 beats per minute.

Systolic pressures of tuberculosis patients as a group varied from a minimum of 60 mm. to a maximum of 276 mm. mercury. The mean pressure was 112 mm. and standard deviation 21.0 mm., representing an average systolic pressure ranging from 91 to 133 mm. mercury.

Diastolic readings varied from 30 mm. to 152 mm. mercury. The mean pressure was 72 mm. and standard deviation 7.6 mm., defining an average diastolic range of 64 to 80 mm. mercury.

Pulse-pressures varied from 10 mm. to 146 mm. mercury. The mean

pressure was 37 mm. and standard deviation 7.7 mm., describing an average pulse-pressure range of 29 to 45 mm. mercury.

A classification of the major tuberculous groups according to blood-pressure range is shown in table 5.

The general run of tuberculosis patients observed in dispensary practice revealed a predominance of normal readings at all pressure levels.

TABLE 5

Blood-pressure range classified according to major tuberculous groups

BLOOD-PRESSURE RANGE	PULMONARY TUBERCULOSIS WITHOUT CARDIORENAL DISEASE		PULMONARY TUBERCULOSIS WITH CARDIORENAL DISEASE		LYMPHATIC AND BONE TUBERCULOSIS		TOTAL	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Systolic								
Absolute hypertension	14	1.0	84	26.9	0	0	98	5.6
Relative hypertension	96	7.1	79	25.3	11	15.3	186	10.7
Normal	662	48.8	106	34.0	5	6.9	773	44.5
Relative hypotension	514	37.9	37	11.9	43	59.7	594	34.1
Absolute hypotension	70	5.2	6	1.9	13	18.1	89	5.1
Diastolic								
Absolute hypertension	2	0.2	45	14.4	5	7.0	52	3.0
Relative hypertension	176	12.9	57	18.3	11	15.3	244	14.0
Normal	845	62.3	140	44.9	24	33.3	1,009	58.0
Relative hypotension	329	24.2	64	20.5	26	36.1	419	24.1
Absolute hypotension	4	0.4	6	1.9	6	8.3	16	0.9
Pulse-pressure								
Absolute hypertension	10	0.7	80	25.6	0	0	90	5.2
Relative hypertension	78	5.8	95	30.5	3	4.2	176	10.1
Normal	614	45.3	89	28.5	30	41.7	733	42.1
Relative hypotension	547	40.3	43	13.8	24	33.3	614	35.3
Absolute hypotension	107	7.9	5	1.6	15	20.8	127	7.3
Total at each pressure level	1,356	100	312	100	72	100	1,740	100

Diastolic pressures showed the highest and pulse-pressures the lowest incidence of such values. The number of normal pressures, however, was relatively less than that attained by normal patients. In uncomplicated pulmonary tuberculosis normal pressures were more common than in pulmonary cases complicated by cardiorenal disease. Lymphatic and

bone tuberculosis patients showed a majority of normal pressures only at pulse-pressure levels.

The great bulk of pressures occurring outside normal limits were found in the range of relative hypotension. Pulse-pressures had the largest and diastolic readings the smallest representation in this zone. The predilection for abnormally low pulse-pressures was seven times greater in tuberculous than in normal patients.

TABLE 6

Blood-pressure range of pulmonary tuberculosis cases classified according to pathological stages

RANGE	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Systolic								
Absolute hypertension	4	0.8	5	1.0	5	1.4	14	1.0
Relative hypertension	41	8.3	37	7.2	18	5.2	96	7.1
Normal	266	53.6	251	48.9	145	41.8	662	48.8
Relative hypotension	168	33.9	195	38.0	151	43.5	514	37.9
Absolute hypotension	17	3.4	25	4.9	28	8.1	70	5.2
Diastolic								
Absolute hypertension	0	0	1	0.2	1	0.3	2	0.2
Relative hypertension	64	12.9	62	12.1	50	14.4	176	12.9
Normal	338	68.2	319	62.2	188	54.2	845	62.3
Relative hypotension	93	18.7	130	25.3	106	30.5	329	24.2
Absolute hypotension	1	0.2	1	0.2	2	0.6	4	0.4
Pulse-pressure								
Absolute hypertension	5	1.0	4	0.8	1	0.3	10	0.7
Relative hypertension	28	5.7	35	6.8	15	4.3	78	5.8
Normal	226	45.6	241	47.0	147	42.4	614	45.3
Relative hypotension	203	40.9	205	40.0	139	40.0	547	40.3
Absolute hypotension	34	6.8	28	5.4	45	13.0	107	7.9
Total at each pressure level	496	100	513	100	347	100	1,356	100

Hypertensive pressures predominated in the cases manifesting signs of cardiac or nephritic lesions. Relative hypertensive pressures prevailed in coexistent mitral disease; and absolute hypertensive pressures in complicating aortic regurgitation or chronic nephritis. All components of arterial tension were involved in this respect, particularly systolic and pulse-pressures. A majority of the systolic readings fell in the range of

absolute hypertension, and that of pulse-pressures in the range of relative hypertension. Subnormal diastolic pressures were the rule in aortic regurgitation.

Tuberculosis patients, in general, revealed the greatest degree of variation from normal pressures at pulse-pressure levels.

Of the 1,356 pulmonary cases uncomplicated by cardiorenal lesions 336, or 24.7 per cent, had a positive sputum. Fifty-seven, or 18.2 per

TABLE 7

Blood-pressure range in pulmonary tuberculous cases classified according to clinical stages

RANGE	ACTIVE		QUIESCENT		ARRESTED		TOTAL	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Systolic								
Absolute hypertension	1	0.2	4	1.2	9	1.7	14	1.0
Relative hypertension	16	3.2	26	8.0	54	10.3	96	7.1
Normal	196	38.9	152	46.7	314	59.7	662	48.8
Relative hypotension	254	50.4	125	38.3	135	25.7	514	37.9
Absolute hypotension	37	7.3	19	5.8	14	2.6	70	5.2
Diastolic								
Absolute hypertension	0	0	1	0.3	1	0.2	2	0.2
Relative hypertension	66	13.1	43	13.2	67	12.7	176	12.9
Normal	291	57.7	206	63.2	348	66.2	845	62.3
Relative hypotension	145	28.8	76	23.3	108	20.5	329	24.2
Absolute hypotension	2	0.4	0	0	2	0.4	4	0.4
Pulse-pressure								
Absolute hypertension	1	0.2	4	1.2	5	0.9	10	0.7
Relative hypertension	15	3.0	14	4.3	49	9.3	78	5.8
Normal	176	34.9	131	40.2	307	58.4	614	45.3
Relative hypotension	250	49.6	151	46.3	146	27.8	547	40.3
Absolute hypotension	62	12.3	26	8.0	19	3.6	107	7.9
Total at each pressure level	504	100	326	100	526	100	1,356	100

cent, of the 312 pulmonary cases with associated valvular heart and nephritic disease showed tubercle bacilli in the sputum. A comparison of the blood-pressure range in tuberculous cases, grouped according to negative-sputum and positive-sputum findings, did not reveal any appreciable difference.

The range of arterial tension, according to pathological and clinical stages of pulmonary tuberculosis, is shown in tables 6 and 7.

The highest incidence of normal pressures was noted in minimal and moderately advanced stages, and the lowest in far-advanced cases of tuberculosis. The number of subnormal systolic and diastolic readings increased progressively from minimal to far-advanced stages. There was a uniform percentage of subnormal pulse-pressures in all stages of the disease. Abnormally low or absolute hypotension pressures were relatively more common in far-advanced than in minimal or moderately advanced cases. In other words, deviations from normal pressures, especially systolic and pulse-pressures, were most pronounced in far-advanced pulmonary tuberculosis.

Arterial tension also varied in the different clinical stages of tuberculosis. The incidence of normal pressures increased with the evolution of the disease from the active to the arrested stage. Relative hypotension pressures became more prevalent with the development of clinical activity.

TABLE 8

Comparative mean pressures and standard deviations obtained in instrumental check-up based on alternate blood-pressure readings in 62 tuberculosis patients

	SYSTOLIC		DIASTOLIC		PULSE-PRESSURE	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Anaeroid manometer.....	107	±13.8	72	±6.5	42	±10.8
Mercury manometer.....	107	±14.0	72	±7.4	42	±10.9

The same was true for absolute hypotension pressures. Pulse-pressures showed the greatest and diastolic pressures the least deviation from normal levels in all stages of the disease. Systolic and pulse-pressure readings, therefore, prevailed at subnormal levels in the active stage of pulmonary tuberculosis.

In summing up, it may be stated that in minimal, arrested stages of pulmonary tuberculosis there was an approximation to normal values for each component of arterial tension. Deviation, especially from normal systolic and pulse-pressure levels toward the range of relative and absolute hypotension, was conspicuously evident in the active, far-advanced stages of the disease. The tendency for blood-pressure variability, furthermore, was influenced more by clinical activity than by pathological extent of tuberculous lesions.

INSTRUMENTAL CHECK-UP

One of the normal determinants of blood-pressure is the integrity and adjustment of the measuring instrument. Calibrated anaeroid sphyg-

momanometers are generally considered less reliable than mercury manometers. The instrument used in this investigation was checked with the aid of a standard mercury manometer. Comparative readings were first made with the two hooked up in tandem. Identical measurements were obtained at varying pressures. The two instruments were then used alternately on 62 tuberculous patients.

A summary of average pressures and standard deviations in their cases is revealed in table 8. It will be noted that the mean pressures were similar, and deviation from the average for each component of arterial tension was slightly less when measurements were obtained with the anaeroid manometer. The resultant blood-pressure range was, however, practically identical.

CONCLUSIONS AND COMMENT

Blood-pressure is a variable under normal and disease conditions.

Normal variations of arterial tension are primarily influenced by individual sex, age and weight. Relative to these factors, the pulse-pressures of norms show greater stability than diastolic or systolic pressures. The latter tend to deviate furthest from normal levels. Systolic variability is affected in greater degree by age and sex than weight. Mean systolic pressures in children are lower than in adult life. In women under 40 years of age, systolic pressures average 10 mm. less, and, after 40, 10 mm. higher than those of men.

A greater divergence from the range of absolute normal pressures is noted in tuberculous than in normal patients of the same sex, age and weight. Pulse-pressures manifest the widest variations chiefly at the expense of systolic pressures. Deviations from normal arterial tension are directed mostly toward hypotension levels. Hypotension, however, is not an absolute rule in tuberculosis. In the dispensary patients studied, the majority of all readings for each component of blood-pressure fell within normal limits. This is accounted for by the presence, in 39 per cent of the cases, of clinically arrested tuberculosis in which normal or quasinormal pressures are prevalent.

The trend of hypotension pressures in tuberculosis is toward relative hypotension rather than absolute hypotension levels. The tuberculosis cases showed an incidence of 34.1 per cent of systolic readings in the range of relative hypotension as compared with 19.6 per cent of similar pressures in the norms. There was an incidence of 5.1 per cent of systolic pressures at absolute hypotension levels in tuberculous subjects;

and 0.2 per cent of such pressures in normal individuals. The majority of authors place 110 mm. Hg as indicating arterial hypotension. In this study, the norms attained an average systolic pressure of 112 mm. with a standard deviation of 5.3 mm. Hg. Taking the standard deviation (*D. I.* equals *1*) as the range of absolute normal, and three times the standard deviation (*D. I.* equals *3*) as the inner limit of absolute abnormal, the minimum level of normal systolic pressures in these cases would be 107 mm. Hg, and the inner boundary of absolute abnormal systolic pressures would be 96 mm. Hg. The inner limits of relative hypotension systolic pressures occur between these minimum extremes. Systolic pressures of 96 mm. or under in adults averaging 23 years of age (the average age of the present norms) are essentially pathological and as such may be termed absolute hypotension pressures.

Conspicuous hypotension pressures are predicated on either pathological extent or clinical activity of tuberculous lesions. Of the two factors, clinical activity is the principal determinant. Progressive lowering pressures, especially pulse-pressures, parallel tuberculous activity, the degree of which is enhanced as the disease approaches the far-advanced stage.

Hypertensive pressures are the rule in tuberculous cases complicated by cardiovascular or nephritic disease. Deviations from normal pressures are directed toward both relative and absolute hypertension levels. Relative hypertension pressures prevail in the cases complicated by mitral lesions, and absolute hypertensive pressures in those with coexisting aortic regurgitation or chronic interstitial nephritis.

The practical import of these considerations is their application in the diagnosis, prognosis and treatment of tuberculous patients.

From a diagnostic point of view, blood-pressure observations are chiefly useful as clues or as confirmatory facts in the evaluation of clinical data. The deviation index serves as a convenient yard-stick in determining whether any particular pressure falls within normal or abnormal limits. Doubtful pressures, that is, those having a deviation index between ± 1 and ± 3, require correlation with physical, roentgenological or laboratory findings. Continued supervision of dispensary patients permits the systematic study of arterial tension in individual cases, and the observation to a certain extent of the evolution of tuberculous lesions from activity to clinical arrest, or *vice versa*. The blood-pressure record is, therefore, a valuable adjunct in the periodical reclassification of tuberculosis patients.

With reference to prognosis, the trend of recurrent individual measurements toward normal findings speaks well for ultimate arrest of the disease. A progressive lowering of blood-pressure, especially pulse-pressure calls for a guarded prognosis.

The management of tuberculosis patients, based on a program of rest or exercise, discontinuance or resumption of employment, preference of dispensary supervision or sanatorium care, depends in no small measure on information derived from the individual blood-pressure record.

SUMMARY

Blood-pressure variations in tuberculosis cover a wider range than under normal conditions. The nature, extent and directional trend of these variations are determined by the degree of clinically active lesions, or presence of cardiorenal complications.

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SPONTANEOUS PNEUMOTHORAX[1]

A Report of 31 Cases

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In 1903 Emerson (1) surveyed the subject of spontaneous pneumothorax and listed 358 references. Since then, with the development of the X-ray as an additional means of diagnosis, the number of cases reported has increased enormously. Before the nineteenth century the presence of air in the pleural cavity had been recognized surgically, but the condition had not been considered clinically important. In 1803, Itard (2) first used the term *pneumothorax* to designate the existence of air in the pleural cavity; he reported three cases from his own experience and one from Selle and one from Bayle. All five were first diagnosed at autopsy. Laennec (3) in 1819 discussed the clinical aspects of pneumothorax, and its recognition in the living patient. The foundation of our knowledge of pneumothorax rests on the studies of Itard and Laennec. Pneumothoraces may be divided into two groups: (1) those resulting from trauma whether accidental or intentional; and (2) those resulting spontaneously from some pathological process in the individual. Traumatic pneumothoraces were the first to be recognized clinically; Riolan (4), Littre (5), Meckel (6) reported cases of air in the chest following trauma. Hewson (7) first mentioned the possibility of air in the chest as the result of a tuberculous perforation.

The pathological conditions which may produce spontaneous pneumothorax are extremely numerous. Laennec (3), Saussier (8), Biach (9), West (10), Morse (11), Ayer (12), and Stoloff (13) have tabulated and discussed the pathological anatomy of pneumothorax. All place tuberculosis at the head of the list; some authors, such as Weber (14), believe that all pneumothoraces which cannot be explained on the basis of some other definite morbid change are due to the rupture of an area of healed tuberculosis. Acute pulmonary conditions, such as pneumonia, empyema, lung abscess, pulmonary gangrene, bronchiectasis, emphysema, pulmo-

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nary infarct, and hydatid disease have been recognized as causes of spontaneous pneumothorax. Extrapulmonary conditions, such as perforation of a gastric ulcer through the diaphragm, perforation of an oesophageal ulcer, perforation of a subphrenic abscess may produce pneumothorax. In some cases no cause can be discovered; these are the cases classified as *idiopathic*. Wood and Vinson (13a) have called attention to spontaneous pneumothorax complicating cardiospasm. In children pneumonia, lung abscess and foreign-body inhalation are frequent causes of pulmonary perforation. The type of spontaneous pneumothorax most commonly seen by a physician depends, in part, upon the type of patients cared for by him. In a tuberculosis sanatorium or in a general hospital with a heavy tuberculosis service, a high percentage of the spontaneous pneumothoraces will be found to be due to tuberculosis. In a series of cases collected from general practice or even from the office and consultation practice of a specialist in tuberculosis and diseases of the chest there will be a higher percentage of nontuberculous spontaneous pneumothoraces.

Our series of 31 cases may be divided into three groups: (1) 10 cases which were definitely tuberculous in origin; (2) 2 cases secondary to asthma and pulmonary fibrosis; and (3) 19 cases without demonstrable underlying pathological change.

TUBERCULOUS SPONTANEOUS PNEUMOTHORAX

Biach (9) in his comprehensive study of 918 cases of pneumothorax collected from the literature and from the records of three Vienna hospitals found tuberculosis accounting for 77.8 per cent. West (10) in 101 cases from the records of the City of London Hospital for Diseases of the Chest found that all but two were clearly tuberculous and that the two remaining were presumably tuberculous. Morse (11) found 70 per cent of his series of 51 cases were definitely tuberculous. Ayer (12) found 69 per cent of the seventy-two cases he tabulated were tuberculous. Stoloff (13), Fisher (15), Palmer and Taft (16) state that 80 to 90 per cent of adult spontaneous pneumothoraces are due to tuberculosis. The proportion of patients suffering from tuberculosis who during the course of their disease develop spontaneous pneumothoraces has been variously stated. Biach (9) found this condition in 1 per cent of 58,731 cases. Gaillard (17) found 36 cases of pneumothorax among 3,415 cases of tuberculosis in the various French hospitals on January 22, 1896. Weber (18) states that 3.5 to 10 per cent of all cases of phthisis develop pneumo-

thorax and that the incidence of spontaneous pneumothorax found in necropsies on tuberculous patients is 10 per cent. Among 5,500 outpatients Olbrechts (19) states that spontaneous pneumothorax was seen seventeen times. Only five could be shown to be due to tuberculosis. Emerson (1), Ayers (12), and Wilson (20) found that pneumothorax is prone to occur in rapidly spreading disease and during acute exacerbations of chronic or quiescent disease. So striking is this that Weil (21) in 1886 stated that he had never seen one develop in afebrile tuberculosis. Ayer (12) found that the majority of his cases occurred within six months after the clinical recognition of the tuberculosis. Wilson (20) reported 50 per cent occurring within two years of the onset of clinical symptoms. The majority of the cases of tuberculosis are far advanced when pneumothorax occurs. Wilson (20) found 84 per cent occurred in far-advanced disease. Oechsli and Skillen (20a) and Beardsley (20b) have reported cases of tuberculosis with spontaneous pneumothorax who presented acute abdominal symptoms.

West (10) states in his conclusions that "of the cases with pneumothorax 75 per cent die within the first fourteen days, about 90 per cent before the end of the month, though the duration of life in the remaining 10 per cent may be considerable." Stokes (22) made the clinical observation that in some patients pneumothorax was followed by, at least, temporary improvement in symptoms. Houghton (23) (24) reports a case in which a patient with far-advanced tuberculosis improved sufficiently after pneumothorax to return to work for some weeks; the patient was later readmitted to the hospital and died of his tuberculosis. Kahn (25) cited a case of complete tuberculous consolidation of the right lung with severe symptoms in which a spontaneous right pneumothorax was followed by arrest of the disease. Stewart (26) reported the case of a patient with far-advanced bilateral tuberculosis in which artificial pneumothorax had been discussed but was not attempted. The patient developed spontaneous pneumothorax on the right side followed by marked improvement in symptoms. Barlow and Thompson (26a) called attention to the frequency of small pneumothoraces in tuberculosis and assembled a large number of references on the subject of pneumothorax.

In a summary of 10 cases of tuberculous spontaneous pneumothorax the ages range from sixteen years to sixty. There are 6 males and 4 females in the group. In 6 cases the spontaneous pneumothorax was one of the terminal factors in a case of hopelessly advanced pulmonary tuberculosis. Death in these cases came a few days or weeks after the develop-

ment of the pneumothorax. One patient, *L. M.*, with far-advanced tuberculosis had survived his pneumothorax for nearly two years. There was still a definite hydropneumothorax present on the left side with marked shift of the heart, mediastinum and trachea to the left. A needle was inserted in the left chest and a high negative-pressure reading was obtained on the manometer. A small amount of air and straw-colored fluid were aspirated from the left chest, and air was injected until the manometric reading became only slightly negative. The patient stated that he felt marked relief from his dyspnoea after the injection of the air. On fluoroscopy the heart, mediastinum and trachea had shifted to a more normal position.

A. B. and *J. McE.* had minimal tuberculous lesions of which the spontaneous pneumothorax gave the first clinical sign though from the appearance of the lungs on X-ray the lesions had been present some time. Patient *A. B.* was put on partial rest for six months. She returned to active employment in ten months and soon afterward broke down with clinical tuberculosis, for which she remained under treatment for eighteen months. She now has apparently arrested pulmonary tuberculosis.

In the case of *J. McE.*, it was decided to maintain his pneumothorax artificially. The patient returned for only five refills. Since then we have been unable to trace him.

A. S. developed a seemingly idiopathic spontaneous pneumothorax in 1923. X-ray films at that time showed no evidence of pulmonary pathological involvement. The patient gave a history of close family contact with tuberculosis. He was not seen for five years, at the end of which time he had haemoptysis. The X-ray films revealed moderately advanced pulmonary tuberculosis with extensive infiltration in the first and second interspaces on the left side (the side of the pneumothorax five years before). Artificial pneumothorax was instituted on the left side and continued for nearly four years. Six months before left pneumothorax was discontinued a small but definite area of infiltration was seen in the right first interspace. This patient has remained under close clinical observation and when last seen the area of infiltration on the right side was clearing slightly. Hamman (27) reported a similar case in which the patient first developed spontaneous pneumothorax on the right in 1909, then on the left in 1910. In 1913 he developed clinical tuberculosis with positive sputum. In 1909 both the tuberculin test and sputum examination were negative.

SPONTANEOUS PNEUMOTHORAX SECONDARY TO ASTHMA

Since the time of Laennec, emphysema has been a recognized pathological condition which might result in spontaneous pneumothorax. Kahn (28) reported the case of a male, aged thirty-six, with a history of asthmatic attacks. During an acute attack he developed the symptoms of spontaneous pneumothorax. X-ray examination, one month later, showed a total collapse of the left lung. The air was absorbed slowly, but, after the aspiration of 800 cc., finally absorbed with complete expansion of the lung and clinical recovery. Nash (29) reported a fatal case of spontaneous pneumothorax and surgical emphysema following influenza. The patient developed acute asthma the day before the pneumothorax occurred. Spivak (30) reported a case of spontaneous pneumothorax in a patient 11 years of age with a history of bronchial asthma since the age of two. The Pirquet and sputum examinations were negative. In October, the X-ray showed left pneumothorax with generalized peribronchial thickening and fibrosis. A second X-ray examination in January showed the pneumothorax still present and larger than on the previous examination. Symes-Thompson (31) reported a case of recurrent spontaneous pneumothorax in a patient with asthma, in whom there was no evidence of pulmonary tuberculosis on X-ray. Fisher (15) reports a case in a male aged 39. The spontaneous pneumothorax followed a severe attack of asthma. Emerson (32) reports a case of bilateral pneumothorax occurring in a female aged 22, with a history of asthma since $2\frac{1}{2}$ years of age. The tuberculin test was negative. Postmortem examination revealed air in both pleural cavities, emphysema of the left lung, and the right lung completely collapsed.

We may summarize 2 cases of spontaneous pneumothorax with asthma. *T. G.* did not have a definite diagnosis of asthma, but his history was strongly suggestive, and the diffuse pulmonary fibrosis, as shown by X-ray, is similar to that frequently seen in asthma and resembling that described by Spivak. Intracutaneous and sputum tests were negative. *E. C. H.*, a female of twenty-one years, gave a history of bronchial asthma since the age of twelve. No X-ray was taken in her case, but repeated fluoroscopic examinations showed a gradual expansion of the collapsed lung.

IDIOPATHIC SPONTANEOUS PNEUMOTHORAX

The diagnosis of idiopathic spontaneous pneumothorax is often disputed. Weber (14) believes that so-called idiopathic cases result from

the rupture of healed tuberculous lesions. Idiopathic collapse occurs most frequently in young males. It is usually followed by reëxpansion of the lung and clinical recovery, so that autopsy examinations in these cases are extremely rare. With the increasing use of tuberculin, we may say at least that certain cases are not tuberculous. Emphysema is rare in the age-group in which this type of collapse is most frequent. The usual explanation of an apparently idiopathic spontaneous pneumothorax is that a small emphysematous bulla has ruptured or that a pleural adhesion has torn. A higher percentage of cases of idiopathic collapse is seen in office than in hospital or sanatorium practice. Biesenthal and Snyder (33) report 12 cases seen in private practice. Olbrechts (19) found that 9 of 17 cases of spontaneous pneumothorax seen in outpatient service were idiopathic. Heck (33b) reported 5 cases of spontaneous pneumothorax occurring among college students, but none exhibited evidence of tuberculosis either at that time or up to the date of graduation. Kjaergaard (33c) discusses spontaneous pneumothorax in apparently healthy persons, and calls attention to the fact that very frequently this condition had nothing whatever to do with tuberculosis. He is of the opinion that such patients should be spared the loss of time and the expense of sanatorium treatment, as well as the fear of pulmonary tuberculosis. He suggests that spontaneous pneumothorax in the apparently healthy be designated as *pneumothorax simplex*.

Palmer and Taft (16) reported 2 cases of spontaneous haemopneumothorax and commented upon the rarity of this condition. Housden and Piggot (33a) report the case of a man of forty-four years, who, following an attack of coughing, developed severe pain in the left chest. He later showed signs of internal haemorrhage and pneumothorax. At postmortem examination the left lung was found collapsed and the left pleural cavity was filled with blood. The source of the blood was thought to be from torn adhesions.

Summarizing two of our cases of spontaneous haemopneumothorax, *L. M.* had a history of family exposure to tuberculosis. A specimen of fluid aspirated from his chest was sent to the laboratory for examination. It contained necrotic material and red blood cells. No tubercle bacilli were found. This patient was last seen by us on August 26, 1932, at which time he complained of pain in his right chest. X-ray examination showed a residual pneumothorax at the extreme left apex, with diaphragmatic adhesions on the left side. No evidence of parenchymal infiltration was seen on either side. The second patient, *A. N.*, had been in ap-

parently good health before the onset of his haemopneumothorax. Fluid was aspirated from his chest repeatedly and used for guinea-pig innoculation, but up to the present time the guinea pigs have shown no evidence of tuberculosis. He has served in the World War and transferred from our care to a Veterans Bureau Hospital, where his collapse has been maintained artificially. He feels well except for a dull ache in the left side of his chest.

Spontaneous pneumothorax is comparatively rare below the age of fifteen. In the early literature cited by Emerson (1) several cases of tuberculous spontaneous pneumothorax in this age-group are described. Scott (33d) gives a summary of the literature from 1829 to 1928. He lists 177 cases in the age-group, birth to fifteen years. He also reports 4 cases from his private practice. His paper presents a most interesting discussion of spontaneous pneumothorax in childhood and adolescence. It contains an excellent bibliograpny. The most frequent causes of spontaneous pneumothorax in children are pneumonia, lung abscess and foreign bodies. Hudson (34), Ross (35), Sanderson (36), and Chadburn and Joseph (37) report cases of postpneumonic spontaneous pneumothorax. Stoloff (13) collected 84 cases from the literature and his own experience, and tabulated them. The cases in his experience were secondary to pneumonia. Stein (38), Smith (39), and Donahoe (40) have reported cases in infants. Stein reviews four cases from the literature; in two delivery was normal and in two difficult. Two patients died within a short time; two survived.

A case of ours, of spontaneous pneumothorax, occurred in a child of one year. The child gave a history of never having been well. The first X-ray examination showed a right pneumothorax. Two months later X-ray films showed complete reëxpansion of the lung, with no evidence of parenchymal pathological involvement. The tuberculin test was positive.

Many authors have reported cases of recurrent spontaneous pneumothorax. Hawes (41) reported a case in which the first pneumothorax was on the right. The lung reëxpanded. Six months later the left lung collapsed. The left lung reëxpanded, to collapse again two years later. The patient was examined at Saranac Lake, where pleural adhesions in the right lower lobe and calcified tubercles in the right lung were the only indications of any pulmonary pathological process. Hawes considers this case to be of questionable tuberculous origin. Watson and Robertson (42) reported 3 cases of recurrent spontaneous pneumothorax.

In one case there were 8 recurrences in five years. X-ray films taken when the lungs were expanded showed no evidence of pulmonary disease. In the second case, there were two collapses in eight months. In the third case, there were 14 collapses and at one time both lungs were partially collapsed simultaneously. The authors believe it wise to consider such pneumothoraces tuberculous until they can be proved otherwise. Laufer (43) reported one case in which there was a recurrence of a left spontaneous pneumothorax after five years. In this case the intracutaneous test was positive. Locke (44) reported one case in which there were 18 recurrences in seven years, and a second case in which there was one recurrence in one year. Two years later, X-ray films of case two revealed an apparently normal chest. Batten (45) reported one case with a recurrence five years after the first pneumothorax. Hirschboeck (46) reported 7 recurrences in a woman in twenty-one months: each recurrence came during a menstrual period. There was no demonstrable pulmonary involvement. Atwood (47) reported a case in which right pneumothorax occurred thirteen years after left pneumothorax: the patient had an uneventful recovery from both pneumothoraces. Wood (48), in an analysis of 71 cases from the Mayo Clinic, found that 21 per cent had definite histories of multiple attacks; 24 per cent had histories suggestive of multiple attacks; in 11 per cent both right and left pneumothorax had occurred, and in 4 per cent there had been simultaneous bilateral pneumothorax. He reported one case with bilateral apical tuberculous infiltration in which simultaneous bilateral pneumothorax occurred.

McMahon (49) found less than 30 cases of simultaneous bilateral spontaneous pneumothorax in the literature. One of his cases with left pneumothorax presented a collapse on the right side before the left lung had completely expanded. After six weeks, both lungs had reëxpanded. Bedford and Joules (50) reported one case with a large pneumothorax on each side, and in which 550 cc. of air were aspirated from the right side. Six months later both lungs were expanded and there was no evidence of pulmonary disease. Emerson's (32) case of bilateral pneumothorax has been discussed. LeWald (51) reported one case with right pneumothorax, followed one week later by left pneumothorax. Four weeks later both lungs were expanded and apparently normal. Meyer (52) cites a case of bilateral pneumothorax with autopsy findings of sarcoma of the kidney with generalized metastases. There was, besides, tuberculosis of the mesenteric lymph nodes. Both lungs contained thin-walled transparent vesicles: the alveoli were dilated and the bronchi

normal. A small metastatic tumor was found in the right lower lobe. Miller (53) and Lamont (54) reported cases of possible tuberculous origin. Benedict (54) cited 3 cases which terminated in death. Two occurred in far-advanced tuberculosis; one in influenza.

In summarizing two cases of recurrent spontaneous pneumothorax, and one of simultaneous bilateral spontaneous pneumothorax, we find that *W. W.* had a recurrence of a left pneumothorax within five months and he is still under the care of his family physician. *O. T.* had a right pneumothorax in December, 1928, and a left pneumothorax in October, 1929, with the tuberculin reaction negative. *L. B.* developed bilateral spontaneous pneumothorax five days after a radical antrum operation; this case has been reported in greater detail by Hinckley (56).

Many cases of unilateral spontaneous pneumothorax of unexplained origin have been reported. Biesenthal and Synder (57) found 200 cases recorded in the literature, and reported 12 cases from their practice. Fisher (15) reported two cases with apparently complete recovery. Kahn (58) reported one case in which three Pirquet tests were negative, and the X-ray one month later showed no pulmonary process. Long and Bray (59) reported 8 cases of spontaneous pneumothorax, including two of tuberculous origin; in one the history was suggestive of tuberculosis, but no pulmonary disease was demonstrable; and in five there was no evidence of pulmonary involvement. Olbrechts (19) found 14 cases of idiopathic spontaneous pneumothorax among 5,500 out-patients. Palmer and Taft (16) cited 4 cases; Rowan (60) called attention to 2 cases; and Terry (61) reported one case with recovery in five weeks. LeWald (62) reported one case in which pneumothorax persisted ten years, and another in which it has persisted more than one year.

In our group of 13 cases of unilateral spontaneous pneumothorax, there were included one female and 12 males, their ages ranging from 15 to 32 years, with 10 cases twenty-two years or below. There was one case at twenty-five, one at twenty-six, and one at thirty-two. Tuberculin tests had been applied in eleven cases, of which six reacted positively and five negatively. In all of these cases the X-ray films showed no evidence of parenchymal pulmonary involvement. All showed marked clinical improvement with relief of symptoms, as the pneumothorax was absorbed and the lung expanded.

Large cavities, pleural cysts, gas in a distended stomach, subphrenic abscesses containing gas, diaphragmatic hernias, and subcutaneous emphysema are sometimes mistaken for pneumothorax. Brown (63), Zan-

dren (64), Warner (65), and Evans (66) discuss the significance of annular shadows in roentgenograms. They believe that such shadows should be considered to be cavities unless proved otherwise. They suggest the use of serial X-ray films taken in various positions, and films after the injection of iodized oil to differentiate between cavities and localized pneumothoraces. Fishberg (67) reported 7 cases in which he diagnosed localized pneumothorax on physical and X-ray examination. Two of these cases came to autopsy and both proved to be large cavities. Two of our cases, *H. D.* and *L. S.*, were diagnosed as spontaneous pneumothorax. The X-ray report in the case of *H. D.* was "large pneumothorax occupying the upper portion of left chest, the base of the lung being adherent." After air was injected and the pleural surfaces separated the large cavity was plainly visible. *L. S.* gave a history of dry cough, fever, and loss in weight. X-rays were taken which were interpreted by the roentgenologist as showing spontaneous pneumothorax on the left. The physical findings were those of a large cavity in the left apex. Air was injected into the left pleural space and the outline of a large cavity was clearly seen.

SUMMARY

Of the 10 patients with spontaneous pneumothorax of tuberculous origin, six were males and four females. The ages ranged from sixteen to sixty years. Six patients with far-advanced tuberculosis died within a few days or weeks of the occurrence of the pneumothorax. One patient with far-advanced disease had survived his pneumothorax for two years when we first saw him in September, 1932. He is still living, and has improved clinically since the marked negative pressure on the side of the collapse has been relieved by the injection of air at regular intervals. We were unable to follow up one case of incipient pulmonary tuberculosis with spontaneous pneumothorax. One case of apparently idiopathic spontaneous pneumothorax was followed five years later by clinical tuberculosis. This patient is handling his disease well and is working full-time. One case of incipient pulmonary tuberculosis with spontaneous pneumothorax, four years after her collapse, has an apparently arrested pulmonary tuberculosis and is working full-time.

Two cases, one male and one female, were secondary to bronchial asthma. We have been unable to determine the present condition of these patients.

In 19 cases of undetermined aetiology, there were 8 negative and 7

positive intracutaneous reactions, and in four no test was recorded. This group included 17 males and two females, whose ages ranged from one to thirty-three years. In 2 cases blood and air were present together in the chest-cavity. In one of these the pneumothorax has been maintained artificially, while, in the other, the lung has failed to expand completely, although nearly three years have passed since the last aspiration of the chest. In the remaining 17 cases, there has been a reëxpansion of the collapsed lung, followed by clinical recovery from symptoms. In one case a calcified nodule with calcified draining lymph nodes was shown in the reëxpanded lung; in the remaining 16 cases no evidence of parenchymal infiltration was seen on X-ray examination.

CONCLUSIONS

1. Spontaneous pneumothorax occurs more frequently than a survey of the literature would lead one to expect.

2. The diagnosis of spontaneous pneumothorax must be confirmed by the aspiration of air from the pleural cavity, or by X-ray films or fluoroscopic examination.

3. Many, but not all, spontaneous pneumothoraces are tuberculous in origin.

4. A higher percentage of idiopathic spontaneous pneumothoraces are seen in office and consultation practice than in hospital or sanatorium practice.

5. Idiopathic spontaneous pneumothorax in apparently healthy individuals is usually followed by reëxpansion of the collapsed lung and clinical recovery from symptoms.

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CLINICAL FEATURES OF PULMONARY TUBERCULOSIS

A Clinical Analysis of 1,099 Consecutive Cases Discharged from the Cook County Hospital Tuberculosis Wards during 1932[1]

ELLIS B. FREILICH AND OSCAR B. RAGINS

In a previous publication (1) a correlation of clinical diagnostic and pathological findings in pulmonary tuberculosis was attempted, on the basis of autopsy findings in 893 cases. In this article we wish to record some of the clinical data in 1,040 consecutive cases of pulmonary tuberculosis.

Of the 1,099 cases admitted to the tuberculosis wards of the Cook County Hospital within a period of twelve months (some of the admissions dating back to the latter part of 1931) there were (table 1):

TABLE 1

Pulmonary tuberculosis cases of various stages	1,040
Miliary tuberculosis	3
Open lymph-node tuberculosis	2
Pott's disease with multiple sinuses	1
Cases admitted as pulmonary tuberculosis but proved to be nontuberculous	53

It will be noted that the error in clinical diagnosis on admission was relatively small, taking into consideration that 26 of the 53 cases proved to be some type of pulmonary condition. These nontuberculous cases were discharged as follows (table 2):

TABLE 2

Carcinoma of lung	8
Lung abscess	2
Empyema	3
Bronchiectasis	4
Bronchopneumonia and lobar pneumococcic pneumonia	3
Unresolved pneumonia	1
Chronic bronchitis	1
Upper respiratory infection	1
Asthmatic bronchitis	1

[1] From the Cook County Hospital and the Department of Medicine, College of Medicine, University of Illinois, Chicago, Illinois.

TABLE 2—*Concluded*

Thickened pleura	1
Silicosis	1
Decompensated heart	3
Hypertensive heart disease	2
Aneurysm of thoracic aorta	3
Coronary disease	1
Hodgkin's disease	1
Thyrotoxicosis	2
Carcinoma of stomach	2
Cerebrospinal syphilis	3
Uraemia	1
Brain tumor	1
Lymphoblastoma of mediastinum	1
No pathological changes found	7

In table 3 the clinical diagnosis on admission is given. Classification of cases was based on standards laid down by the National Tuberculosis Association. The clinical diagnosis was corroborated practically in all cases by positive roentgenological findings, positive sputum, or both. In this series of 1,040 cases, there were 750 cases with positive sputum at one time or another.

With regard to the sputum findings in tuberculosis we wish to emphasize that really active cases of pulmonary tuberculosis with persistently negative sputum are rare. In most of these cases, if examined repeatedly, the presence of tubercle bacilli will be noted in the sputum. We are in accord with Fishberg (2) that it is doubtful whether a patient who shows persistently negative sputum is in fact sick with tuberculosis requiring treatment.

One will also readily note in this table the high percentage of moderately advanced and far-advanced cases. They can simply be explained by the fact that the tuberculosis wards of the Cook County Hospital have no admission restrictions for any type of pulmonary tuberculosis, irrespective of the stage, as long as there are vacant beds. Very frequently patients are brought in a moribund state.

TABLE 3

Diagnosis on admission

Total Cases		1,040
Minimal tuberculosis	44	
Moderately advanced	406	
Far advanced	590	

TABLE 4

Racial distribution of cases

Total Cases		1,040
Colored	410	
Mexicans	46	
Chinese	5	
Filipinos	2	
White	577	

In table 4 it is noted that the colored and Mexicans represent a much higher percentage of admissions to the tuberculosis wards of the Cook County Hospital than their corresponding number of population in Chicago and Cook County. Mendelsohn (3) has found that the number of admissions of tuberculous Mexicans to the Cook County Hospital was fourteen times as great as in the general population, including the great number of colored population in Cook County; also that the tuberculosis death-rate among the Mexicans in Cook County is six times as high as the average death-rate in the general population.

With regard to morbidity and mortality of tuberculosis in different races, it has been shown (4) that tuberculosis is not uniformly distributed among the different peoples of the earth. Even in the same time and place, the incidence of tuberculosis and its death-rate differ widely between the different groups of the population. The rôle of acquired resistance to tuberculosis has also been repeatedly emphasized. The peoples showing a low tuberculosis mortality are those who have received their infection during childhood and overcame it, while groups of people that show a high tuberculosis mortality are those that reach maturity without having been exposed to such immunizing infection and are therefore lacking in this acquired allergic response. Their course of phthisis is more rapid and fatal.

There is no doubt, however, that the environment and occupation of the Mexicans may be a strong causative factor in the morbidity and high mortality of pulmonary tuberculosis among them. Their home conditions are the most unfavorable and undesirable. In spite of the hard work they perform their income is usually meagre and their diet is affected accordingly.

TABLE 5

Age-distribution

AGE	NUMBER OF CASES
10–15	9
15–20	81
20–25	146
25–30	186
30–35	164
35–40	145
40–45	96
45–50	70
50–55	68
55–60	40
60–65	15
65–70	17
70–75	1
75–80	1
80–85	1

The youngest of the patients was 13. The oldest was 83. Table 5 shows a gradual rise in the disease from the age of 10, reaching its full height at 30, and then followed by a gradual decline.

Table 6 shows the number of male and female patients.

TABLE 6

AGE	MALE	FEMALE
10–20	34	56
20–30	201	131
30–40	190	119
40–50	109	57
50–60	77	31
60–70	26	6
	637	400

In our series there were 396 females and 644 males. Table 6 shows the relatively higher morbidity in females than males up to the age of 20, which is in accordance with recently compiled statistics, and is explained by the fact of greater participation of young girls in industry. Another explanation lies in the dietary fads which young girls practice to keep their weight down.

Table 7 enumerates the various tuberculous complications that were encountered in the series of 1,040 cases of pulmonary tuberculosis.

TABLE 7

	NUMBER	PER CENT
Tuberculous laryngitis	143	13.70
Tuberculous glossitis	5	0.48
Lymph-node tuberculosis	9	0.86
Miliary tuberculosis	4	0.38
Tuberculous cold abscess	7	0.67
Effusions in chest	27	2.60
Tuberculous empyema	3	0.29
Tuberculous lung abscess	2	0.18
Tuberculous enteritis	249	24.00
Tuberculous enteritis with perforation	4	0.38
Fistula-in-ano	22	2.12
Tuberculous peritonitis	31	2.98
Tuberculous kidney	5	0.48
Tuberculous epidydimitis	10	0.96
Tuberculous cystitis	2	0.18
Bone tuberculosis	14	1.34
Tuberculous otitis	2	0.18
Follicles	1	0.09
Marked clubbing	3	0.27
Thrombophlebitis	4	0.38
Complications that were the immediate cause of death		
Fatal haemoptysis	14	1.34
Spontaneous pneumothorax	11	1.06
Tuberculous meningitis	22	2.12

In studying the various complications and their frequency in pulmonary tuberculosis, especially those of tuberculous laryngitis, enteritis and peritonitis, a marked discrepancy was noted in their frequency as recorded in table 7 and our previous work (5) on tuberculosis post-mortem material, which is naturally more reliable. This perhaps explains also the marked discrepancy in the frequency of these tuberculous as well as other complications in pulmonary tuberculosis, as recorded by various authors (6).

Haemoptysis: The frequency of haemoptysis in known cases of pulmonary tuberculosis varies. Some authors give it as low as 20 per cent, while others put it as high as 80 per cent. Lawrason Brown concludes that probably one-half of all patients with pulmonary tuberculosis have

haemoptysis at some stage of their disease. At the Phipps Institute in Philadelphia, 49.9 per cent of their pulmonary-tuberculosis cases had haemoptysis at some time. The cause of great differences in the percentage of haemoptysis recorded by the different authors is probably due to the difference as to what they classify as haemoptysis, whether it is merely blood-streaked sputum or a frank haemorrhage of one-half ounce or more. In our 1,040 cases, there were 374 cases of haemoptysis, or 35.8 per cent. Fourteen of these proved to be fatal haemoptysis and even attempted pneumothorax collapse failed to stop them.

Some of the nontuberculous complications associated with pulmonary tuberculosis in our cases that we wish to mention were:

Diabetes Mellitus: The incidence of tuberculosis in diabetes mellitus, according to the complete data of Golden, Joslin, Wilder, Adams, Fritz, Wendt and Peck, and Murphy (7), based on the observation of 8,500 patients, is 2.6 per cent, that is, about three times higher than the average tuberculous morbidity in the United States between 1920 and 1929 inclusive. The course of tuberculosis complicated by diabetes is not necessarily fatal, if the diabetes and tuberculosis are properly treated. In our series there were 19 cases complicated by diabetes and of these fourteen died, four were discharged as apparently arrested, and one as quiescent.

In regard to cardiac complications in pulmonary tuberculosis in this series, while there were recorded some 23 cases of myocardial insufficiency or myocardial failure, probably as the result of tuberculous toxaemia or pulmonary insufficiency, there were only two cases recorded with valvular heart disease. This is in accord with the belief that any cardiovascular disease which tends to produce passive congestion of the lung is a preventive of tuberculosis.

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A SUCCESSFUL METHOD OF CULTIVATING TUBERCLE BACILLI[1,2]

M. E. COWEN AND E. J. HENDERSON

In submitting this communication regarding the cultivation of the tubercle bacillus, we make no claim of originality for the method. We have combined certain parts of several previously reported methods in an attempt to produce a medium and a technique which would give us 100 per cent constant growth from known positive sputa, and, at the same time, be more free from contamination.

Although the subject may be considered a hackneyed one, we have felt that we would be making a worth-while contribution to the work of diagnosis if we could put such a procedure at the disposal of small laboratories or small sanatoria which are not equipped for animal inoculation and which, like ourselves, have had discouraging results in previous attempts at cultivation.

This method is not expensive and it is not beyond the capability of any well-trained laboratory technician. In it we have paid close attention to two important details; the sterilization of all utensils and the final sterilization of the medium after being tubed. The results obtained have been very much better than with any other method we have tried and we believe that, to a great extent, these precautions have been responsible for them.

We have obtained a culture in every tube seeded with known positive sputum (288 tubes from 72 specimens) and we were congratulating ourselves on the fact that we had found contamination in only 4 tubes out of 1,265 (approximately 0.3 per cent), when the accidental tipping of a batch of tubes receiving their final sterilization allowed the medium to touch the cotton plugs in about 75 per cent of them and 11 of the 55 tubes (20 per cent) developed contamination, bringing our total to 15 out of 1,320 (approximately 1.2 per cent).

The medium is a modification of Petragnani's, as recommended by Saenz and Eisendrath (1), in which asparagin is substituted for the pep-

[1] From the Pennsylvania State Tuberculosis Sanatorium, Cresson, Pennsylvania.
[2] Approved for publication by the Secretary of Health, State of Pennsylvania.

tone of the original formula. In preparing it, we have followed closely the general directions given by Norton, Thomas and Broom in their excellent report concerning the Petragnani medium (2).

Our formula for making about 120 tubes (150 mm. x 15 mm.) is as follows:

450 cc. milk (cream removed)
18 gm. potato flour
2.6 gm. asparagin
225 gm. potato (peeled and sliced thin)
12 eggs
3 egg-yolks (additional)
35 cc. glycerine C. P. (sterile)
30 cc. 2 per cent aqueous solution of malachite-green

Put the sliced potato, the potato flour and the milk into a double boiler and dissolve the asparagin in the mixture. Cook for two hours, stirring constantly until the mixture becomes sticky; then stir occasionally.

Sterilize the eggs by rubbing with alcohol and flaming. Break the whole eggs into a sterile 2-litre Erlenmeyer flask, add the extra yolks and shake well, breaking the yolks with a sterile glass rod if necessary. Use a sterile cork or rubber stopper in the flask while shaking. Add the glycerine and the dye solution and shake again.

Cool the potato-milk mixture to 45–50°C.; add the egg-glycerine mixture slowly, stirring thoroughly; and filter through sterile gauze into a sterile beaker. The medium thus prepared is neutral to litmus.

The shaking of the flask causes a very persistent, fine-bubbled foam, which should be removed by skimming with filter paper or with a sterilized piece of fine wire-gauze; otherwise the slants will have an undesirable porous surface. The medium, in 4- or 5-cc. quantity, as desired, is now poured into culture-tubes which have been sterilized with their cotton plugs inserted. The cotton plugs are replaced and covered with rubber caps instead of with paraffin.

As recommended by Norton and his co-workers, we have made the final sterilization of the tubed medium in an Arnold sterilizer. The tubes are arranged in a slanting position in the cold sterilizer, and care must be taken that they do not slant enough to bring the medium into contact with the cotton plugs. Nearly a year ago we had decided that our few contaminations had occurred in tubes of that kind, and we discarded

them constantly until the time of the previously mentioned accident in connection with the sterilization of a small batch of tubes. That accident upset our good record in contaminations but seems to have confirmed our opinion as to the cause of them.

The sterilizer is heated slowly to 80°C., which should require about one and one-half hours, and the temperature should not be permitted to go much beyond that point. It can be controlled easily by the opening and closing of the sterilizer door.

It has been our practice not to let the temperature get above 45° during the first half-hour and from 45° to 65° in the second half-hour; reach 80° at the end of the third half-hour; and then hold it at that point for twenty minutes.

Apparently this sterilization is one of the most important steps in the preparation of the material. Von Huth and Lieberthal (3) warn strictly against the use of too much heat in the making of Hohn egg-medium, and we have found that too little heat at this stage produces slants which are too soft and "mushy" for use. A few tubes from each batch should be incubated as a test for sterility. The fact that we have not been obliged to resterilize any of our medium points to the value of the aseptic preparation and emphasizes Norton's statement, that "reheating, even at 80 degrees, reduces the growth-promoting properties of the medium used."

Cerruti (4) advises that when the material to be examined is suspected of containing a bovine strain of tubercle bacilli, two sets of cultures should be made, in one of which bovine bile is substituted for the glycerine of the Petragnani formula.

PREPARING THE SPECIMEN

If there is a considerable quantity of sputum, take about 1 cc. from the bottom of the container, from the purulent or mucopurulent part of the specimen and place it in a sterile petri dish. Add from 1 to 2 cc. of 5 per cent oxalic acid, depending upon the consistency of the sputum, thick, mucopurulent or purulent specimens requiring the larger quantity. We have thought it not advisable to use more than 2 cc. in any case, as there seemed to be a tendency to retard growth when it was done. Macerate thoroughly with a small, sterile instrument. We use sterilized wooden applicators. Pour into a sterile centrifuge-tube and place in the incubator at 37.5°C. for one-half to three-quarters of an hour, shaking occasionally.

At first we used 6 per cent sulphuric acid, neutralized a few minutes

later by 4 per cent sodium-hydroxide solution, leaving the treated specimen slightly alkaline to litmus when seeded upon the medium but there appears to be little difference in the effect upon the culture and the oxalic method is easier and quicker.

On removing the specimen from the incubator, add sterile normal salt solution until the tube is nearly full; mix, centrifugate and pour off the supernantant liquid except about 2 cc. which is mixed thoroughly with the sediment. A slide is then made from the sediment-mixture for the usual staining and microscopic examination. If no tubercle bacilli are found in this stained specimen, the material remaining in the centrifuge-tube is seeded upon four tubes of medium, either by means of a sterile pipette or, if the material be very thick, by a flamed wire loop. We have found that by seeding four tubes from each specimen we greatly increase our chances of finding the bacilli if only a few of them are present.

HANDLING THE CULTURE

The seeded tubes are now placed in covered tin cans and incubated at 37.5°C. We feel that not enough emphasis has been put upon the necessity of protecting cultures of tubercle bacilli from the action of daylight, especially during the first week or ten days, and we believe that numerous failures in attempts at such cultivation have been due to lack of this precaution. Subsequent inspections of the tubes for evidence of growth should be done quickly and the cultures returned to the covered cans with as little delay as possible.

After being incubated for about ten days, the cultures are carefully examined and, if the surface appears suggestive of a growth, a slight scraping is made for a slide which is stained by the usual methods. In this way a diagnosis often is possible before the appearance of definite colonies, but it must be remembered that such scraping with the wire loop may remove the only growth on the surface of the slant and prevent later confirmaton of the diagnosis.

From all the known positive specimens of sputum which we have seeded upon this medium, growth has appeared in from seven to eighteen days. From 185 specimens of sputum negative to our customary direct-smear and concentration methods, we have obtained positive cultures in 27, or 14.5 per cent. In these cultures the minimum time for the appearance of easily recognizable growth was ten days, and the maximum, 44 days. The colonies are of pin-head size or a little larger, rounded, and of a brownish-yellow color which renders them clearly visible against the green

in the medium. In very luxuriant growth they soon form an irregular coating on the surface of the slant. All tubes are kept in the incubator 60 days before being reported as "no growth."

Thirty-three specimens of material other than sputum gave the following results:

20 urines: 19 positive on direct examination and culture.
1 negative on direct examination but positive on culture.
1 spinal fluid: no growth. Later reported "nontuberculous."
1 blood: no growth (Mantoux test negative to 1 mgm. O.T.).
3 pleural fluids: 1 positive growth, 16 days.
2 no growth.
1 pus from wrist: positive growth, 20 days.
3 pus from cervical glands: 1 positive growth, 25 days.
2 no growth.
1 peritoneal fluid: no growth.
3 faeces: no growth.

No animal inoculations have been done in connection with this work; therefore we cannot offer any opinion as to its comparative value. However, we have been led to these conclusions because (1) the method here described is giving us better results than any other we have tried; (2) it is not difficult and it affords the small laboratory a valuable aid in the diagnosis of tuberculosis; (3) it emphasizes the value of asepsis in the preparation of the medium.

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THE TIME-INTERVAL BETWEEN PRIMARY INFECTION AND SUPERINFECTION AS A FACTOR IN IMMUNITY TO TUBERCULOSIS[1]

An Experimental Study

HENRY SEWALL, EUGENE DE SAVITSCH AND CHARLES P. BUTLER

In a recent communication we reported the local effects in guinea pigs of subcutaneous infection with pure cultures of virulent tubercle bacilli, followed by superinfection at various intervals ranging from one to many days (1). We were impressed with two different categories of effects attributable to superinfection.

One concerned the character of the immediate local inflammatory phenomena at the site of inoculation; the other was determined by the remote and general effects of superinfection upon the welfare of the animal organism.

We will refer to the former as *allergy* and to the latter as *immunity*.

Our observations had seemed to indicate that, with a given bacillary dosage, superinfection following infection after 53 days tended to cause more intense local inflammatory reaction,—oedema and redness,—than at other intervals.

On the other hand, when superinfection was imposed at various wider intervals, up to about 130 days, there was decided evidence that the effect upon the well-being of the animal, as shown by clinical condition when alive and by the signs of conservative tissue reaction at autopsy, was somewhat notably more favorable when superinfection followed infection after about 70 to 90 days.

In the present essay we attempt to represent the relations of allergy and immunity through a statistical study of tissue reactions due to superinfection following infection at various intervals of time.

We lament the paucity of material supporting important conclusions, but insurmountable obstacles oppose a present repetition of our experiments on a larger scale.

The difference in behavior between normal and tuberculous guinea pigs following inoculation with virulent tubercle bacilli is an ancient theme but of perennial interest in tuberculosis.

[1] From the National Jewish Hospital, Denver, Colorado.

Baldwin and Gardner (2) showed how voluminous was the literature on the subject up to their own publication of 12 years ago. These authors studied particularly the reactions of guinea pigs to inoculation with virulent tubercle bacilli as modified by previous infection with an avirulent strain of similar germs, which had been introduced in various ways, resulting in the production of a chronic, static disease.

In addition to authorities already quoted we would note the interesting dermal studies of Nasta (3) leading to important general conceptions, and to those of Boquet (4) treating of the reactions of tuberculous guinea pigs to superinfection according as its route is cutaneous, subcutaneous or testicular.

All workers agree on the characteristic differences between the vital reactions of animals to infection and reinfection, respectively, but there still lacks unanimity on the meaning of the difference, and especially whether it has definite purposive foundation.

We know of no study of the subject precisely along the lines which we have followed.

METHODS

The pure cultures of tubercle bacilli used by us were of the human strain, had been isolated by Dr. H. J. Corper from sputum some 12 years before, and had since been propagated on artificial media, both glycerine-agar and Petroff's gentian-violet, through semimonthly subcultures. A decade ago the cultures caused progressive tuberculosis in guinea pigs inoculated subcutaneously with doses of 0.000,000,001 (1-billionth) mgm. Tested for infectivity several times a year by our colleague, Dr. M. Cohn, the cultures, incubated about 6 weeks, were found throughout the period of our work infectious for guinea pigs in subcutaneous dosage of 0.000,001 (one-millionth) mgm. or less.

Our experimental subjects were young male guinea pigs generally weighing 300 to 400 gm. Inoculations were made subcutaneously on either side of the lower abdomen.

We will present separately the protocols of two series of experiments, 1 and 2, and then describe their results together under specified topics.

EXPERIMENT 1

Twenty-four guinea pigs were subcutaneously infected each with 0.1 mgm. virulent tubercle bacilli, August 18, 1931. Half of these served as a control group (*d*). The remainder formed two equal experimental groups. The 6 members of group (*a*) were superinfected on the opposite side 53

days after infection; the remaining group (*b*) was similarly superinfected 74 days after infection. The bacillary dosage for superinfection was identical with that used for infection, that is, 0.1 mgm.

EXPERIMENT 2

Thirty-six young male guinea pigs were subcutaneously infected each with 0.01 mgm. of the pure culture of tubercle bacilli, August 11, 1932. Half of these animals were reserved as a control group (*d*). The remaining 18 guinea pigs were divided into equal subgroups, (*a*) 53, (*b*) 74, and (*c*) 95. The figures indicate the number of days elapsing between infection and superinfection in the 3 groups.

Unfortunately in both 1 and 2, a single animal of the terminal experimental group died before the date of reinoculation. These might well have been numbered among the controls, but they were excluded from the records. It should be emphasized that the final comparisons between the experimental (superinfected) and the control (infected) groups contrast animals which had received very different numbers of tubercle bacilli; the proportions were: in experiment 1, as 2 to 1; and in 2, as 11 to 1.

We shall now under six heads briefly differentiate by their reactions the various groups of experimental guinea pigs from one another according to the intervals elapsing between infection and superinfection, and compare them with the control animals of the corresponding experiments.

1: THE INTENSITY OF ALLERGIC REACTION AT LOCUS OF SUPERINFECTION AS A FUNCTION OF THE TIME-INTERVAL SEPARATING SUPERINFECTION FROM INFECTION

Superinfection was regularly performed in skin depilated the previous day over an area of 2–3 cm. sq. on the lower abdomen and opposite the site of infection. The reaction to superinfection was pronounced within 24 hours and was perhaps maximal in 48. The intensity of reaction was measured by the tint of pink color in the skin and the prominence, extent and hardness of the swelling. Examinations were recorded daily or at frequent intervals until the local changes subsided.

Experiment 1: On the whole, the inflammatory color was deeper and more persistent and the swelling greater following superinfection in group (*a*), 53 days, than in (*b*), 74 days.

Experiment 2: We arrived at the surprising impression that superinfection

with 0.1 mgm. bacilli following infection with the same amount, as in experiment 1, causes rather a *less* violent inflammatory reaction than does a similar superinfection following infection with one-tenth the dose, or 0.01 mgm., as in experiment 2. Comparing in the latter the intensities of reaction to superinfection in our 3 experimental groups ((*a*) 53 days; (*b*) 74; and (*c*) 95 days), we find obviously graded violence from (*a*) downward to (*c*).

As we shall show, in each experiment the animal-group superinfected after the longest interval was incontestably the more immune-resistant as regards the disease; we find, especially in experiment 2, that (*caet. par.*) ***host-immunity is somewhat inversely proportionate to the intensity of local allergic reactions.***

2: LOCAL ULCERATIONS OF THE SKIN AS FOUND AT AUTOPSY

1: (a) 6 guinea pigs. Ulcer on side of superinfection only, 2; ulcer on both sides, 4.

(b) 5 guinea pigs. No ulcer, 1; ulcer, side of infection only, 3; ulcer both sides, 1.

(d) 12 controls. Ulcer side of infection, 12.

2: (a) 6 guinea pigs. Ulcer side of infection only, 2; ulcer side of superinfection only, 2; no record, 2.

(b) 6 guinea pigs. Ulcer side of infection only, 3; ulcer both sides, 3.

(c) 5 guinea pigs. No ulcer, 2; ulcer side of infection only, 3.

(d) 18 controls. Ulcer side of infection, 16; no record, 2.

Results: Single primary infection invariably causes local ulceration in our controls. Superinfection, according to the interval at which it follows, may cause healing of extant ulcers or failures to produce new ones, as in 1 (b) and 2 (c).

3: SUPPURATION OF REGIONAL LYMPH NODES AS FOUND AT AUTOPSY

1: (a, 6) Pus absent, 1; pus in inguinal lymph nodes, both sides, 5; (in one case multiglandular).

(b, 5) Pus absent, 3; pus in inguinal lymph node on side of infection, 2.

(d, 12) Controls. Pus present in inguinal lymph nodes of one or both sides, occasionally multiglandular, in 10; inguinal nodes without pus but severely infected, 2.

2: (a, 6) Pus absent in 3; pus in inguinal lymph nodes both sides, 1; pus on side of infection, 1; side of superinfection, 1.

(b, 6) Pus absent in 1; pus both sides, 1; pus on side of infection, 4.

(c, 5) Pus absent in 4; pus on side of infection, 1.

(d, 18) Controls. Pus absent 4; pus on both sides, 4; pus on side of infection, 8; caseous both sides, 2.

("Multiglandular" implies involvement of other than the inguinal lymph nodes, such as, *iliacs, sternals,* etc.)

Results: In experiment 1, the 12 control animals (*d*), infected with a single dose of 0.1 mgm. bacilli, all presented macroscopic, extensive lymph-node changes, with suppuration in 10 cases; while the two experimental groups, receiving a total of twice the bacillary dose, showed for (*a*), superinfected after 53 days, pus absent in one case, though bilateral in 5. However, in group (*b*) in which superinfection was withheld for 74 days, host-protection was marked, for the regional nodes remained intact in 3 of 5 cases and broke down only on the side of infection in 2.

In experiment 2, the infective dose was but one-tenth the former, namely 0.01 mgm. Accordingly, we find that in group (*d*) of 18 control guinea pigs four continued free from macroscopic lymph-node suppuration while in 14 cases the breakdown was obvious. Contrasted with this result, of the 6 guinea pigs of group (*a*), superinfected after 53 days with 10 times the initial dose, half the animals remained free from lymph-node suppuration, and in the still more remarkable instance of group (*c*), in which superinfection was withheld for 95 days, when 10 times the infecting dose was administered, 4 of 5 guinea pigs remained free from lymph-node suppuration.

The conception arises that the influence of superinfection is not limited to preventing the breaking down of tissues but is effective in the resolution of lesions already extant. We have already expressed the opinion (1) that the local subcutaneous abscess which, according to our regimen, invariably follows superinfection, in well-immunized cases becomes regularly more or less completely absorbed.

It is expedient at this point to consider the implications of *quantity* of infecting material. We assume that, broadly speaking, the effect of superinfection upon the host is determined by the grade of immunological education, so to speak, acquired by the tissues as a result of infection. Our observations suggest a somewhat direct relation between the quantity of antigen and the speed of immunological accomplishment.

Contrasting, for example, the results of superinfection in our two experiments, we find that in 1 there has developed a very marked immunological host-protection in (*b*), 74 days after infection; this character is not confined to lymph-node integrity but is shared by all other functions we have studied. But, turning to experiment 2, with one-tenth the infecting dose, we find in group (*c*), superinfected after 95 days, a closer

immunological resemblance to group (*b*) of experiment 1 than has the group (*b*) of experiment 2, superinfected at the same interval.

4: THE LENGTH OF LIFE FOLLOWING INFECTION IN THE RESPECTIVE ANIMAL GROUPS

1: All 24 animals died of tuberculosis except 4, which were chloroformed, while in fair to good condition, about 390 days after infection; one of these was from group (*b*), superinfected after 74 days, and 3 were from the group of controls, (*d*).

The number of guinea pigs dying in each group, with average of days lived after infection, was as follows: (*a, 6*), 246; (*b, 4*), 332; (*d, 9*), 216.

In group (*b*), one guinea pig had died before superinfection and one was killed.

Adding to (*b*) and (*d*), respectively, credits for the long life of animals chloroformed, the averages become: (*b, 5*), 343 days; (*d, 12*), 305 days.

It must be remembered that the experimental groups, (*a*) and (*b*), received twice the bacillary dosage of the controls (*d*), for each member of the former got 0.2 mgm., and of the latter, 0.1 mgm.

The results distinctly show a stronger average hold on life among the superinfected animals as compared with the controls, and this is very notably so in group (*b*), superinfected after 74 days. The good showing made by the 3 control guinea pigs which were killed could give a false impression of their vitality; according to standards announced in the next section, the resistance of these animals had reached its final break preceding *exitus*.

2: Owing to the relatively small infecting dose (0.01 mgm. bacilli) 5 of the 18 control guinea pigs remained alive for about 390 days, when they were chloroformed. The average length of life in the 13 controls which died was 255 days; including the 5 guinea pigs killed, the average length of life was, for the 18 controls, 292 days.

Of the 17 animals of the experimental groups 12 died after an average length of life of 252 days; as in the controls, 5 remained alive 390 days after infection and were then killed. Two of these belonged to subgroup (*b*) and 3 to (*c*). Following is a condensed statement in which each subgroup is bracketed with its number of animals, then in the 3 experimental divisions is noted in italics the number of days at which superinfection followed infection, and finally the average length of life in days for each subgroup following infection. In (*b*) and (*c*) the figures for length of life are corrected to include the actual life-terms of the animals killed:

(a-6) *53*, 267; (b-6) *74*, 278; (c-5) *95*, 339; (d-18), controls 292.

In the experimental groups we find the life-periods steadily increasing from (*a*), superinfected after 53 days, when the average life was 267 days to (*c*), superinfected after 95 days and with an average life of 339 days. It must be remembered that each experimental animal received a total bacillary dosage 11 times that of each control.

5: RELATION OF BODY-WEIGHT TO INFECTION AND SUPERINFECTION AND IN PROGNOSIS

Frequent weighings of our animals was a routine practice and this procedure proved suggestive of metabolic-immunological relations.

When young, actively growing guinea pigs are inoculated with virulent tubercle bacilli the rate of growth would seem to casual observation to proceed unchanged. We were obliged to definitely test this question to ascertain that growth was impeded by developing infection. In a special inquiry of 12 male guinea pigs, average weight about 300 gm., 6 were given subcutaneously 0.1 mgm. virulent tubercle bacilli. Frequent comparisons of the weights of the normal and infected animals through several weeks disclosed no striking difference, but it was found at the end of 35 days following infection that the inoculated animals had made an average gain of less than 31 per cent in weight while the normal controls had gained over 59 per cent.

The characteristic weight-curve of a fast-growing guinea pig infected with tuberculosis rises rather steeply to a maximum and is maintained for a variable period in a more or less undulating plateau, showing slight alternate losses and gains in weight; but, as exitus approaches, there is a more or less steep and constant fall in the curve which may cover several months preceding death.

But our tables of body-weights convey a suggestion of immunological interest as to the temporary effect of superinfection upon the weight-curve according to the interval at which the second inoculation follows the first.

In experiment 1, with the large infecting dose of 0.1 mgm. bacilli, in group (*a*), superinfected after 53 days, it was found a week later that 5 of 6 guinea pigs had lost 20 to 30 gm. each in weight. In group (*b*), superinfected after 74 days and tested in the same way, 2 guinea pigs showed little or no change in weight while 3 showed a gain of 10 to 35 gm.

In other words, it appears that, in an animal, infection initiates a defi-

nite progressive series of vital relations designed to protect it against the harmful effects of superinfection. If superinfection follows prematurely, vital disturbance is the result; if delayed until adequate cellular preparation has been achieved, superinfection may be tolerated without disturbance, or it may even prove host-conservative. This fluctuation in body-weight as an immunity-reaction prompted a special examination.

For instance, 20 young adult male guinea pigs were infected subcutaneously, each with 0.1 mgm. virulent tubercle bacilli. Six served as controls, 7 were superinfected with a like dose after 53 days, and 7 after 74 days.

The results showed that, while primary infection retarded growth but slightly, superinfection after 53 days tended to an immediate loss of weight persisting for a week or two, while superinfection after 74 days caused much smaller loss, or failed to check the normal gain; at the same time 4 of 6 controls increased markedly in weight.

In experiment 2 it happened that our animals were not weighed within 15 days of the first superinfection,—a period sufficient for the recovery from a temporary loss of weight; but instructive results followed an inquiry into the relative percentages of weight gained by the various groups of guinea pigs over a considerable time. For this calculation it was necessary to obtain the average weight of animals in each group at the time of infection and also at some later date, for which we chose a period of 116 days after infection, at which the percentage gain was calculated. As the rate of gain was dependent on the initial weight, the percentage of gain was standardized by a calculation of simple proportion on the assumption that each guinea pig weighed 400 gm. when infected. On this basis the 18 *controls* gained in weight, in 116 days following infection, an average of 87.5 per cent; the members of the experimental groups (*a*), (*b*) and (*c*), superinfected after 53, 74 and 95 days, respectively, gained in order 60, 102 and 160.5 per cent.

That is to say, the gain of weight in the three groups of experimental guinea pigs as compared with the controls agrees perfectly with the conception that superinfection influenced the gain in weight to the effect of a loss in (*a*) and increasing gains in (*b*) and (*c*), all in proportion to the stability of tuberculosis-immunity, as determined by several standards. It so happened, moreover, that 6 of the control guinea pigs in experiment 2 had exactly the same initial weight as 6 of the experimental animals, distributed as (*a*) 3, (*b*) 1, (*c*) 2, through which the foregoing conclusion was essentially verified directly.

Results: We infer an intimate relation between metabolism of the body and its state of immunity to tuberculosis because in the stage of demonstrably incomplete immunity represented in our group *1(a)*, a sudden temporary loss of weight marks the shock of superinfection with tubercle bacilli, which is not observed in group *1(b)*, in which immunity is better developed. Moreover, we find in experiment 2 that the rate of gain in weight in the 3 groups of superinfected animals, as compared with the controls, appears to be intimately related to their status of immunity; namely, in group (*a*), showing high allergy and low resistance, the growth increase is less than that of the controls, while in the groups (*b*) and (*c*) it progressively improves. It may be added that corresponding weight-relations pertained in experiment 1.

6: CLASSIFICATION OF ANIMAL GROUPS ACCORDING TO POSTMORTEM FINDINGS

A: Incidence of effusion

Of the 24 guinea pigs in experiment 1, 20 died naturally and 4 were killed (1 experimental and 3 controls) about 390 days after infection; of the 36 animals in experiment 2, 26 died and 10 were killed (5 experimental and 5 controls) after similar periods.

Most animals dying of disease had developed effusions in one or more of the serous cavities, in which the pericardium was usually included; these exudates were frequently bloody, but seldom purulent. The incidence of effusion is recorded below; the appropriate groups, noted by letter, with the number of animals concerned are in brackets, following which are the percentages in which effusion was found.

I: Bacillary dosage of infection, 0.1 mgm.; dosage of superinfection, 0.1 mgm.
Animals superinfected (11); (a, 6) 83 per cent: (b, 5) 40 per cent.
Controls (d, 12); infecting dose 0.1 mgm., 83 per cent.

II: Bacillary dosage of infection, 0.01 mgm.; dosage of superinfection, 0.1 mgm.
Percentage of animals showing effusion:
Superinfected (17); (a, 6) 50 per cent; (b, 6), 66 per cent; (c, 5) 20 per cent.
Controls (18), infecting dose 0.01 mgm., 39 per cent.

Results: We note the preponderance of effusion among the controls in experiment 1, 83 per cent, as contrasted with the same group in experi-

ment 2, 39 per cent, and align it with the fact that the dosage in experiment 1 was 10 times that in experiment 2. In experiment 1, we note that only in group (*a*), superinfected after 53 days, is the incidence of effusion equal to that of controls. In the highly immune guinea pigs of each experiment, (*b*) of 1 and (*c*) of 2, we find a markedly lower incidence of effusion than in the controls.

We dwell upon the incidence of effusion among our animals with the conception that it is conceivably, indeed probably, a manifestation of allergy. It will be noted that, in experiment 1, 10 of our 12 controls showed effusions of which 3 were haemorrhagic. This was a late phenomenon, probably of terminal significance. The average age at death in the 10 controls was 234 days after infection. Of the control animals, in either experiment, which were killed approximately 390 days following infection only one showed an effusion and this was limited to the pericardium of a guinea pig of experiment 1, which differed from all others of its class in being ill and paralyzed when killed.

The important experimental studies of Paterson (5), begun on rabbits but extended on guinea pigs, confirmed those of Floyd (6) and led to the conclusion that, "Clinical pleural effusions are caused by the infection of an allergic pleura." On the other hand, Corper and Rensch (7) completely failed, in rabbits, to obtain pleural effusions by reason of previous sensitization. There are evidently, at present unknown, key-conditions which should explain the discrepancy.

B: The respective visceral changes in the various animal groups

(*1*) *Visceral changes in the control groups:* There was a marked difference between the visceral responses of the control groups in the two experiments corresponding with the difference in dosage. In experiment 1, infecting dose 0.1 mgm., all 12 control guinea pigs were subjects of generalized advanced tuberculosis except one dying within 173 days. The *postmortem* evidence in nearly every case pointed to an acute inflammatory attack preceding *exitus*. In the 5 controls which survived over 300 days there was a marked development of fibrosis.

This condition was best illustrated in the controls of experiment 2, in which the infecting dose was only one-tenth as large; there seemed here a very obvious struggle against foredoomed ending; often, apparently, healing fibrosis nearly kept pace with tissue destruction.

Splenomegaly, so early and regularly an anatomical result of tuberculous infection in the guinea pig, was but very slightly marked in no

less than 5 of the 18 controls in experiment 2. This was not due to early death, for 4 of the 5 cases were found among the guinea pigs that were finally killed. Macroscopic determination of splenic tuberculosis could not be made with certainty in 3 of the 5 cases, though the evidence in other organs was positive.

(2) *Visceral changes in the experimental groups:* It is here that we find concise evidence for the immunizing force of regulated superinfection. In experiment 1 (*a*), the 6 animals were reinoculated with 0.1 mgm. virulent bacilli after an interval of 53 days. Though this group outlived the controls which died, at autopsy 5 of the 6 animals were indistinguishable from the latter. The remaining animal, which lived 386 days following infection, presented a curious association of effective immunity and a peculiar distribution of lymph-node suppuration. In group (*b*), superinfected after 74 days, the 5 animals showed apparently pronounced signs of organic immunity. The length of life, including 1 killed, was over 340 days. Two cases of very slight visceral involvement were recorded as "almost tuberculosis cures," and two others as "healing;" in one of the latter the lungs contained many discrete and very hard tubercles and in another there was multiple cavitation of the lungs.

In this group, apparently protected specifically against tuberculosis, there was a suspicion of special susceptibility to pyogenic infection, for in 2 cases death was due to cellulitis, extending in one from a suppurating shoulder joint, and in another from a purulent inguinal lymph node.

It must be remembered that the infecting dose in this experiment was nearly a million times the minimal dose capable of causing progressive tuberculosis, and that the superinfected animals received twice the total dose given the controls.

C: Effects of bacillary dosage

As already noted, in experiment 2, all animals received an infecting dose of 0.01 mgm. bacilli, in addition to which the 3 experimental groups, (*a*), (*b*) and (*c*), were superinfected with 0.1 mgm. bacilli at periods, respectively, of 53, 74 and 95 days following infection. Comparing the 3 groups through autopsy records we find from (*a*) to (*c*) a progressive increase in fibrosis and a general decrease in the extent of visceral tuberculosis; when lesions were extensive encapsulation was progressively pronounced. In this experiment there was a notable diminution in both splenomegaly and pathological deposit from (*a*) to (*c*). In 4 of the 5 animals in (*c*) the spleen was estimated as less than twice the normal size,

and in 3 cases as free from macroscopic suspicion of tuberculosis, while in the small spleens of the control group a strong suspicion of tuberculosis prevailed.

Approximately 390 days following infection there remained alive, and in "fair" to "good" condition, 5 of the 17 "experimental" and 5 of the 18 "control" animals. Of the former group 2 guinea pigs belonged to (*b*) and 3 to (*c*).

Four of the 5 experimental animals, though in apparently good clinical condition, had for 1 to 3 months shown a slight, continuous loss of weight; they were therefore deemed to be on their final decline, though still long removed from *exitus*. The remaining animal, however, a member of group (*c*), had reached its maximum weight of 1,100 gm., and with one slight lapse had maintained it, four months before its death by chloroform 391 days after infection. Autopsy disclosed no certain macroscopic visceral tuberculosis; nor even marked lymphatic adenopathy. We again note that in this experiment all superinfected animals received a total bacillary dosage times as great as the controls.

Results: The effect of quantity of bacillary dosage is shown by comparison of the two groups of control animals in which the individual dosage was as 10 to 1. The duration of life in animals receiving the large dose was shortened about 15 per cent; but more striking was the postmortem evidence of acute inflammatory disturbance preceding *exitus* as shown by more or less bloody serous effusions,—more than twice as frequent after the larger dose. In the experimental group we find that the interval at which superinfection follows infection is of paramount importance in determining the anatomical results.

It seems that with the larger infecting dose a certain progress toward immunity is reached earlier than with the smaller dose; in experiment 1, for example, the immunological reaction resulting from superinfection after 74 days resembles more closely the reaction secured in experiment 2, in 95 days, in which the infecting dose was one-tenth the former.

The evidence indicates that fibrosis is more abundant in the experimental than in the control groups and that in the former it not only proportionately preponderates with the lapse of time, but it would appear that in group (*b*) of experiment 1, and group (*c*) of experiment 2, pathological lesions have either been prevented or, when formed, removed under the influence of superinfection. There remains a doubt as to the meaning and influence of complicating pyogenic infections, especially marked late in experiment 1.

SUMMARY AND CONCLUSIONS

Two groups of guinea pigs were inoculated with virulent tubercle bacilli in quantities of 0.1 and 0.01 mgm., respectively, a dosage which may be regarded as considerable in either case. Half the animals of each group were retained as controls. In experiment 1, the infecting bacillary dose was 0.1 mgm. Six guinea pigs were superinfected with the same dose after 53 days, and six after 74 days; 12 controls received only the infecting dose. In experiment 2 the infecting dose was reduced to 0.01 mgm. bacilli, but the dose of superinfection remained 0.1 mgm. and was administered at three increasing intervals, 53, 74 and 95 days, following infection of 3 groups of 6 guinea pigs each.

We have traced and compared the reactions of the various groups of our animals according to six different categories: namely, (1) the intensity of the admittedly "allergic" inflammatory reaction at the site of superinfection; (2) the local ulcerations of the skin as found at autopsy; (3) the prevalence of suppuration in the regional or other lymph nodes as found at autopsy; (4) the length of life following infection in the various animal groups; (5) the relations of body-weight to infection and superinfection and to lethal prognosis; and (6) classification of animal groups according to the visceral changes found at autopsy.

Our results seem to furnish very positive experimental evidence that *superinfection*, a term adopted as less subject to disagreement than *reinfection*, has the power under certain circumstances, not only to increase fibrosis and aid in the segregation of foci of infection, but also to actively stimulate the bodily mechanism to resist the implantation of fresh foci of disease, if not, indeed, to cause the absorption of some foci already formed.

Our results point very positively to a single variable in the experimental problem as of paramount importance in achieving resistance (immunity within the host): this variable is the time-interval elapsing between infection and superinfection.

As a matter of convenience, if not of necessity, we are justified in treating the whole "battle of tuberculosis" from a purposive viewpoint. Krause (8), Willis (9), and others have shown that when a normal animal is inoculated in or under the skin with living tubercle bacilli these probably begin at once to migrate throughout the body. In the several days elapsing between the injection of bacilli and development of the primary nodule of infection at the site of inoculation, tubercle bacilli must have been generally distributed.

It seems probable that they undergo destruction through established general defenses of the body, and we seem justified in assuming that their passage is signalized by the acquirement of a new property by the tissues of the invaded host,—hypersensitiveness to tuberculoprotein. This functional cellular change, devoid of anatomical signs, is doubtless continually intensified under stimulation of infectious foci, far and near. Within a few weeks subcutaneous reinoculation of the same animal causes a much accelerated response in the formation of a local nodule, or, in its absence, violent swelling and destructive inflammation at the site of injection, known as "Koch's phenomenon." Careful study of these changes at the site of reinoculation inevitably suggests that they are coördinated by a purpose. The acute inflammation about the site of superinfection involves, from the mechanical side, local swelling and dilution of toxic material; splinting and immobilizing of the parts, thus limiting lymphatic movement and absorption.

Krause and his colleagues find that the migration of bacilli in the new inoculation is greatly retarded (10). Others show that wholesale destruction of bacilli in the second injection occurs, by lysis or otherwise, or that they are cast off *en masse* in a slough (11).

Recently Rich has demonstrated that the juices of the immune animal (rabbit) quickly immobilize and agglutinate the bacteria (pneumococci) of reinfection, and thus prevent that migration which might occur prior to development of the local allergic inflammatory reaction (12).

These reactions which signalize a hypersensitive state of the host to a specific antigen are not confined to the mere site of inoculation; modified by environment, under similar stimulation they occur throughout the body. Thus Calmette (13) calls attention to the fact that when a suspension of bacteria is injected directly into the circulation of a normal animal the germs may be recovered from the blood for a number of days; but if a second inoculation is made after the animal has acquired hypersensitiveness to them the germs very rapidly disappear from the circulation.

Our experimental data suggest a certain methodology in the development of immunity. Among the credible factors concerned is specific hypersensitiveness of the body tissues toward antigen, which is foreign and presumably injurious to the invaded host. But hypersensitiveness alone could have no protecting value without a motor or efferent auxiliary acting to annul the irritant to hypersensitiveness. The evidence we have presented stresses the importance of the time element in the develop-

ment of this tissue immunity. A guinea pig infected with a certain dose of tubercle bacilli responds with the mobilization of various latent powers of defense. We have noted in our *control* animals how abundantly developed is often the healing fibrosis. That the tissues have developed a new technique in dealing with their enemy is shown by their immediate response to reinfection.

Our experiments indicate that at a certain period after infection the violence of the local reaction to reinfection begins to steadily diminish, but, on the contrary, the general stability of the reacting host,—his power of adaptation and restoration, that is, immunity, at the same time increases. The local inflammation, etc., caused by superinfection at 53 days denotes "allergy." We have found that at this period the whole body probably shares the allergic state,—as shown by the disturbance of the animal's growth. We find that, withholding superinfection for stated periods, allergy diminishes but immunity increases.

Far from stigmatizing allergy as indifferent or antagonistic to the development of immunity we are impressed with the view that it represents crude vital energy, specifically excited and capable of adaptation to the protection of the host whose tissues are trained by stimulation of the very antigen which first aroused them.

In another place one of us has ventured to classify the conditions of combat between host and pathogen under three heads (14): (1) the host-defensive mechanism is relatively so perfect that the invader is destroyed without disturbance,—*perfect immunity;* (2) the virulence of pathogen is relatively overwhelming and the host quickly succumbs,—*defenseless susceptibility;* (3) the two contestants are approximately equal and the outcome of the struggle depends upon the relative allergic resources of the combatants, becoming less acute in proportion as one or the other prevails.

It must be acknowledged that the experimental facts indicate that the stage of high immunity may involve local conditions of hypersensitiveness carrying peculiar dangers to the host. This may be manifested, as in our experiments, by acute multiple cavitation in the lungs.

We venture to consider the results of these simple experiments to have a certain value as elucidating problems in human clinical tuberculosis.

We know the fundamental value of *rest* in allaying active disease in the infected man. At any moment the patient has the power to autoinoculate and to superinfect himself from within by the simple device of muscular activity. Clinical experience amply proves the danger of ill-timed superinfections through exercise.

In fact, the major clinical art is how to secure and to sufficiently maintain completeness of rest.

It should be no small solace to the patient under restraint that, according to the testimony of the experimental guinea pig, his time of durance is not wasted—but rather that every day adds strength to his foundation of immunity;—and also that timely and graded superinfection through muscular exercise itself may *in due season* furnish the natural stimulus to cure; strengthen immunity and resolve pathological deposits.

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A MICRO-MOTION-PICTURE STUDY OF THE GROWTH OF TUBERCLE BACILLI FROM COLD-BLOODED ANIMALS[1] (1)

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The growth in micro-culture of the acid-fast timothy-grass bacillus, *M. phlei*, has been described (2) in a previous publication. The present paper records a similar investigation of several strains of the so-called tubercle bacilli from cold-blooded animals. This study has been carried out by making upon motion-picture film a prolonged series of photomicrographs of the living bacteria. The film thus obtained can be studied at leisure frame by frame or, run through a projector, it gives a motion picture, greatly sped up in time, of the bacterial growth.

Most tubercle bacilli from cold-blooded animals grow better at room temperature (20°–25°C.) than at incubator temperature (37°C.); both the micro-motion-picture apparatus (3) and the preparations were therefore kept in a room held at a constant temperature within this lower range. Under these circumstances growth can profitably be photographed over a period of one to two weeks. The interval between exposures was either two or four minutes. The important optical conditions that were maintained in making the photographs are:

Objective: 3-mm. oil-immersion dark-field objective NA 1.0
Magnification: 330 ×
Film: plain positive
Exposure Time: about 1/5 second
Filter: Jena deep blue no. BG 12.

The micro-preparations were made in the usual fashion as elsewhere described (4). They consisted of organisms growing on the under side of thin blocks of nutrient agar supported on a cover-glass inverted over a hollow slide. Considerable care must be used in sealing these preparations, to ensure that there is no drying over a period of several weeks. This has been satisfactorily accomplished by putting a layer of vaseline

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between the slide and cover-glass, and painting the junction between them thickly with hard (62°C.) paraffin.

Three media have been used for the micro-preparations. One was ordinary nutrient agar containing 6 per cent glycerine and 2 per cent agar; another was the Koch Institute modification (5) of Proskauer and Beck's synthetic medium; the third was a 6 per cent glycerine nutrient agar made with potato water as a base. In order that the last medium shall be microscopically clear it is essential that the potato water be freed from suspended starch granules by settling, by Berkefeld filtration, or by both. The surface of the agar block was seeded with organisms by careful streaking with a minute platinum loop. If this loop carries a suitable number of bacteria, obtained either by preliminary dilution of a bacterial suspension or by wiping the loop after touching it to a colony, there is no difficulty in finding microscopic fields in which the growth of single bacilli can be watched. Success in obtaining ample growth in microcultures depends largely upon how this inoculation is carried out. The surface of the agar must not be too dry nor must too much fluid be added by the loop. It is equally essential that the agar surface be not broken during the streaking. By taking these precautions luxuriant growth has been obtained in more than 90 per cent of the micro-preparations of these tubercle bacilli from cold-blooded animals.

Nine cultures of bacteria have been studied. With them between 4,000 and 5,000 feet of film covering an observation period of roughly 3,000 hours have been made. Two of the strains were supplied by the H. K. Mulford Company through the courtesy of Dr. John Reichel. Of these one was from a salt-water fish, the other from a snake. The remaining 7 cultures were received from Dr. J. D. Aronson of the Phipps Institute. Two were originally isolated from frogs, the rest from a fish, a turtle, a garter snake, a boa and an iguana. All are acid-fast and, except the strain from the garter snake (designated *M. thamnopheos*), they are alcohol-fast. Their present pathogenicities were not ascertained. The turtle strain is a subculture of the well-known Friedmann "turtle bacillus," *M. chelonei*, which has been carried in laboratories for over 20 years. One of the frog strains (called for convenience *M. ranae I*) is a subculture of the almost equally old "frog bacillus" (Rupprecht). The other cultures, all younger than these two, have been isolated from time to time from animals held in captivity. In the present experiments single-colony strains were obtained by the customary methods of dilution plating. Most of these strains are widely different from one another

in their gross cultural characteristics. Some are highly chromogenic; others are entirely colorless. Two were very smooth, one was completely rough, and the others were apparently stabilized at various stages between these extremes.

One of the most interesting features of these acid-fast bacilli is the ease with which certain strains can be dissociated. Most bacteria when dissociated give rise to a rough and a smooth, or a smooth and a mucoid variant. The tubercle bacilli from cold-blooded animals, and apparently all the other acid-fast organisms, differ in that complete roughness and complete smoothness are limiting conditions often not immediately attained. The more rough and more smooth acid-fast strains that then result from dissociation appear as two of an innumerable number of stages that can be imagined as existing between the two extremes.

On solid media the thoroughly smooth acid-fast colony is roundish and regular in outline,—almost hemispherical in shape. Though of a mucoid consistence it may, like the very *S* dissociant of the "frog bacillus," be so fluid that it will drip from the surface of an inverted petri plate. In the usual fluid media these strains grow diffusely, and with no tendency to aggregate either at the surface or at the bottom. Completely rough strains on solid media form heavily convoluted heaped-up colonies which show no tendency to spread over the surface of the medium. On fluids they produce thick pellicles. They never grow diffusely throughout the medium and ordinarily do not grow on the bottom. The intermediate strains differ from these two. Their colonies always have a spreading superficial apron or veil. The extent and consistence of this veil, as well as the shape of the central bacterial mass, vary greatly, depending upon whether the strain is nearer the rough or the smooth extreme. Most intermediate races produce surface growths on fluid media. Some have an extensive veil-like spreading edge; a few when inoculated below the surface grow for long periods of time as discrete granular clumps on the bottom of flasks; one dissociant, from the iguana culture, which was more nearly smooth than rough, always developed diffusely for a few days.

By taking advantage of these widely different modes of growth it is easy to get dissociants from most of the strains listed above. Very smooth races of the frog bacillus were obtained by inoculating a single colony on the body of glycerine-broth or a synthetic fluid medium and making frequent broth-to-broth passages with the cloudy fluid as inoculum. When such a smooth strain was plated for single colonies, one out of several thousand would grow roughly at first. A very rough strain

apparently arising from these occasional spontaneous dissociants was obtained by allowing a fluid culture of the smooth strain in Long's synthetic broth (6) to age. Inoculation from the surface growth, which eventually formed on the surface of fresh fluid, repeated several times and interspersed with dilution platings, gave a strain that was very rough. The same treatment of the turtle bacillus resulted in a very rough strain and one which, while not so fluid as the very *S* frog bacillus, was nevertheless thoroughly smooth. The culture from an iguana, called for convenience *M. iguanae*, gave rise to a rough and to an intermediate dissociant. A single colony from the original culture when planted in fluid medium grew diffusely and at the bottom for a few days; afterward the medium became clearer, and growth continued at the bottom till eventually a pellicle formed. Several surface-to-surface transplants of the pellicle resulted in a moderately rough strain. The smoother strain that was the consequence of frequent transplants from the cloudy fluid grew on solid media as colonies with irregular outlines and broad, spreading aprons. Attempts to derive a thoroughly *S* strain from this inter-

PLATE 1

FIG. 1. A micro-colony of the rough dissociant of the "turtle bacillus," *M. chelonei*, growing on glycerine-agar.

FIG. 2. The same field after growth has progressed. The absence of any tendency of the bacteria to spread over the medium is evident.

FIG. 3. The same field after the bacterial chains had become so long that they were doubling over one another and packing together to form the convolutions which characterize the macroscopic appearance of their colonies.

FIG. 4. A micro-colony of the smooth dissociant of the "frog bacillus," *M. ranae I*, growing on a synthetic medium.

FIG. 5. The field of fig. 4 somewhat later. All the bacteria have not only started to elongate, but they have also moved apart from one another. This is especially apparent in the lower left-hand group of organisms.

FIG. 6. The same field still later. The bacterial pair at the bottom of the left-hand group had just divided in the previous picture. All the bacteria are still further apart than before.

FIG. 7. The same field. When single bacteria have divided they have usually moved apart. Where they have remained end to end in chains, the separation of these chains has continued to increase.

FIG. 8. The same field. Growth and especially division have continued in the bacterial chains. The mucoid substance in which the bacteria are embedded holds their chains as far apart as are the streptococcoid chains of rapidly growing type-III pneumococci.

FIG. 9. The same field after growth has continued till the original bacteria and their progeny have been forced out of view. Apparently due to the rising refractive index of the extracellular substance the bacteria are becoming more and more transparent. This figure is to be contrasted with fig. 3.

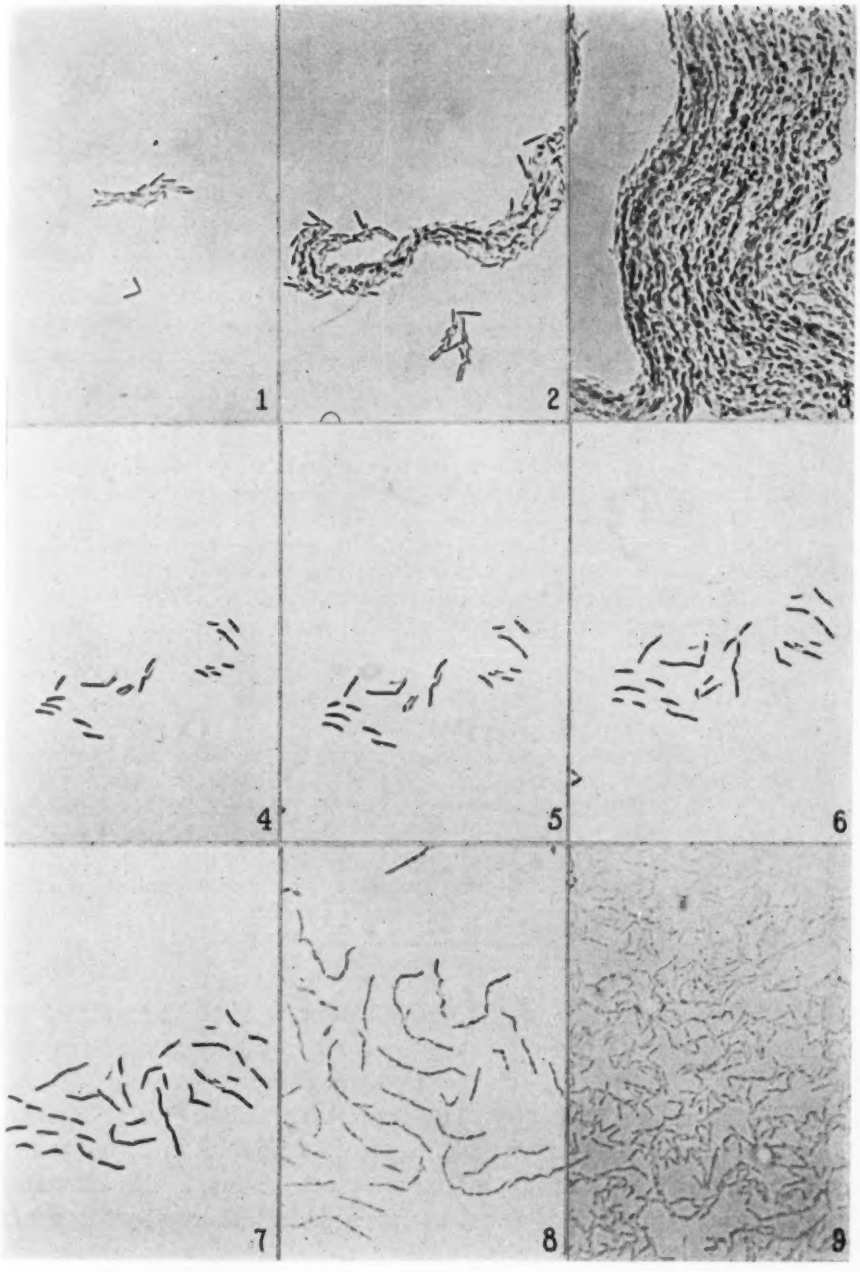

PLATE 1

mediate one were not successful. The boa dissociants were one very rough, and the other intermediate but more rough than smooth. The very rough and chromogenic cultures from the frog (*M. ranae II*) and from the fish have not been dissociated.

Study of these various strains in micro-culture shows why they are so different in their gross-colony morphology. As they grow and multiply, completely rough organisms form long tangled masses and have no tendency whatever to spread over the surface of the nutrient medium (figures 1 to 3). On the other hand, the bacteria of smooth strains lie separately and apart from one another, spread apart as they multiply, and show themselves to be embedded in a mass of more or less viscous

PLATE 2

FIG. 10. Growth of the smooth dissociant of the turtle bacillus, *M. chelonei*. As with the smooth frog bacillus, chains of bacteria are embedded in a large mass of viscous material.

FIG. 11. A micro-colony on glycerine-agar of the boa strain. This dissociant is predominantly, though not completely, rough. As the following picture shows, the organisms form a tangled mass but a few exploring rods grow out from the central mass.

FIG. 12. A later stage in the growth of the micro-colony of fig. 11. Compare with fig. 2.

FIG. 13. A micro-colony of an intermediate but predominantly rough dissociant of the iguana strain.

FIG. 14. A later picture of the field of fig. 13. The growth is somewhat more spreading than is that of fig. 12.

FIG. 15. The micro-colony of fig. 13 after further growth.

FIG. 16. An early stage in the growth of bacteria of the Mulford snake strain on glycerine-agar. The irregular and granular character of many of the bacteria is easily seen.

FIG. 17. The field of the preceding figure at a later time. This strain, though intermediate and predominantly rough in its colony morphology, is smoother than the preceding boa and iguana strains.

FIG. 18. A later picture of the two preceding fields. Note the many bacteria spreading from the central mass over the surface of the medium. Compare with figs. 2 & 12.

material (figures 4 to 9). In the motion pictures of the growth of the frog bacillus, *M. ranae I*, the jelly-like character of this product of the bacterial growth is especially evident. A micro-colony of this organism at first consists of a single bacterium, or of discrete chains of bacteria, separated from one another by distances which are often several bacterial diameters (figure 8). As a result, it closely resembles in appearance a growth of highly encapsulated pneumococci. Though the substance they produce is sufficiently viscous to push the organisms apart from one another, as they grow there is no reason to believe that it constitutes a formed capsule with a fixed boundary. The intermediate types fall into two groups. If they are predominantly rough (figures 11 to 12 & 13 to 15)

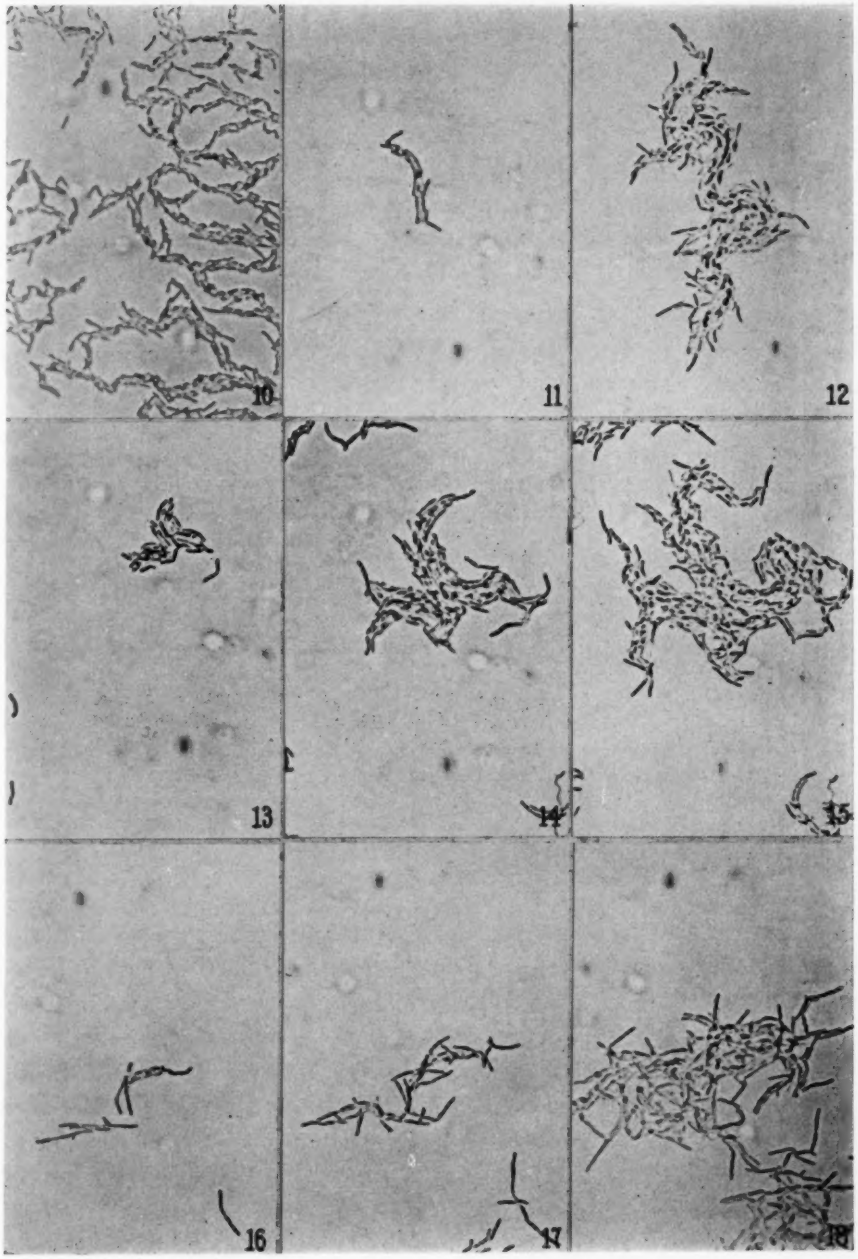

PLATE 2

they will for the most part form the tangled masses characteristic of rough growths, but at the same time they will send out "exploring" groups of organisms upon the surface of the surrounding medium. These explorers are more numerous the less completely rough the culture (figures 16 to 18). Certain of the smoother intermediate strains have lost any pronounced tendency to form tangled growths without acquiring at the same time the ability to produce large amounts of mucoid substance. Their micro-colonies, as a consequence, consist of clusters of organisms lying in one plane but packed closely together (figures 19 & 20).

PLATE 3

FIG. 19. Several organisms of the smoother dissociant of the iguana strain growing on potato-glycerine-agar.

FIG. 20. A micro-colony developed from the bacteria of fig. 19. The organisms show little tendency to form a tangled heaped-up growth, but they do not elaborate the voluminous jelly characteristic of thoroughly smooth strains.

FIG. 21. A micro-colony of the Aronson garter-snake strain on glycerine-agar.

FIG. 22. The field of the preceding figure after several divisions have occurred. This illustrates the short and coccoid forms that are produced in young cultures.

FIG. 23. Organisms from a six-weeks-old culture of a chromogenic frog strain planted on glycerine-agar. Heavily beaded forms are shown at *A* and *B*.

FIG. 24. The field of fig. 23 after growth has taken place. The beaded forms of the preceding figure appear again at *A* and *B*.

FIG. 25. Organisms from an old iguana culture planted on glycerine-agar. A large coccus sprouting at three points is shown at *C*.

FIG. 26. The same field somewhat later. The sprouts from *C* have grown; one has split off a rod which has continued to elongate normally.

FIG. 27. The same field still later. The sprouts from *C* have continued to develop as rods. Soon after this picture was made the coccus apparently ruptured and disappeared completely.

The micro-motion-pictures make it evident that the smooth strains of the tubercle bacilli from cold-blooded animals give typically mucoid growths. It would be natural to infer that these bacteria produce substances which the rough strains have lost the power to manufacture. Either this must be true or else certain substances made by both dissociants differ profoundly in their colloidal properties, the colloid of the smooth bacteria being powerfully hydrophilic, while that of the rough strains is equally hydrophobic. A choice between these possibilities cannot be made in the absence of adequate chemical analyses of the bacteria and their metabolic products.

The micro-photographs provide a way of studying the morphological characteristics of these different cultures of bacteria and of ascertaining

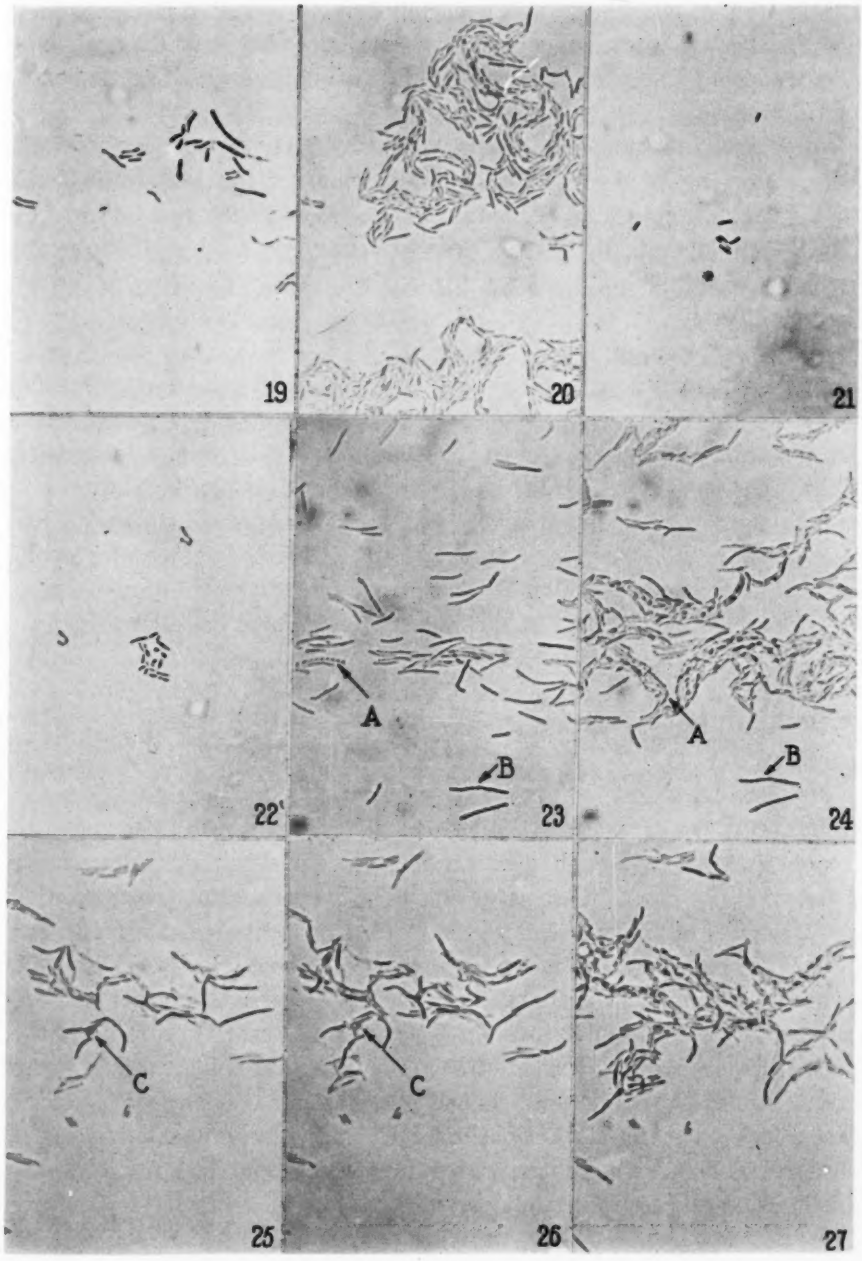

PLATE 3

whether any of them indicate the existence of the so-called bacterial life-cycles. Though there may be minor differences between them all the cultures included in the present study have organisms which are morphologically alike.

A few generalizations can be drawn from a study of their motion pictures. In a healthy and actively multiplying preparation all the bacteria grow as rods that are commonly neither straight nor uniform in length and diameter. They multiply by transverse fission which apparently can occur at any point along their length. The coccoid forms (figures 21 & 22), as seen in young cultures, are due to this tendency of the bacilli to split into unequal parts. As a culture ages such forms become more numerous, owing to the fact that multiplication ordinarily continues long after the stage of active increase in total bacterial volume has passed. Old rods which do not fractionate in this way usually become increasingly irregular in thickness and eventually take on the appearance of a crude string of beads (figure 23). Some of the very short rods slowly round up and swell as they age, producing in this way coccoid forms that are seemingly identical with the more numerous ones found in old cultures of *M. phlei*. When planted on a fresh medium these enlarged coccoid forms have been seen to sprout rods before disintegrating (figures 25 to 27). Heavily beaded forms have never grown (figures 23 & 24); less beaded rods become homogeneous before developing in the usual fashion.

Because of the tangled masses they form it is impossible to follow the growth of rough organisms with the same attention that can be given to the other strains. Rough bacteria are often smaller than those of the corresponding smooth dissociant, and their rods are much more gnarled and twisted. As might be expected from their limited contact with the nutrient medium, their micro-colonies grow more slowly. Branched forms are common in preparations of the very smooth strains and are occasionally seen in rough growths. There is no reason according to the present experiments to believe that important morphological differences exist between the rough and smooth bacteria, nor is there any evidence for assuming a bacterial cycle in the sense of a regularly repeated sequence of morphological changes which must be gone through as a micro-colony increases and its bacteria multiply.

SUMMARY

Micro-motion-pictures have been made of the growth and multiplication of tubercle bacilli from cold-blooded animals living in micro-culture.

Acid-fast bacteria from 9 sources have been used and several dissociants obtained from them. The completely rough strains form convoluted heaped-up colonies on solid media and grow as thick pellicles on fluid media. Photographed in micro-culture their bacteria form a tangled mass and exhibit no tendency to spread out over the surface of the medium on which they grow. The very smooth strains, on the other hand, produce round mucoid colonies on solid media and grow diffusely throughout fluid cultures. Viewed in micro-culture these smooth bacteria grow separately from one another and embedded in a voluminous jelly-like substance which does not exist in rough growths. Strains intermediate between the rough and smooth extremes have modes of growth which also are intermediate. Examination of the motion-pictures shows that rapidly growing preparations consist of bacilli of various sizes which divide by transverse fission only. Since this division often continues long after the stage of rapid growth has passed, old preparations contain many short rods and coccoid forms. On fresh media such cocci grow into rods. There is no evidence of any truly cyclic phenomena.

The writer is indebted to J. R. Lucas for help in carrying out many of the routine bacteriological procedures required by these experiments.

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THE SUSCEPTIBILITY OF CHICKENS TO HUMAN AND BOVINE TUBERCLE BACILLI[1]

WILLIAM H. FELDMAN

It is generally accepted that the domestic hen is very resistant to the organisms of tuberculosis of human or bovine origin (*Mycobacterium tuberculosis hominis* and *Mycobacterium tuberculosis bovis*). This fact is of much significance in distinguishing the human and bovine forms of the tubercle bacillus from that responsible for tuberculous infections of chickens. Although the work of Cadiot, Gilbert and Roger (2) (3), Mohler and Washburn, and others would indicate that under stated conditions certain strains of the tubercle bacillus may exhibit marked variations in their pathogenic behavior in species ordinarily considered resistant, the inability of human and bovine tubercle bacilli to incite in the tissues of chickens a characteristically progressive tuberculous infection in the accepted sense is fairly consistent. The introduction of large amounts of infectious material from cases of human and bovine tuberculosis into chickens by intravenous inoculation is not followed by the development of a disease process comparable to that which occurs when similar material is injected into guinea pigs, or that which develops when chickens are exposed to infective material obtained from cases of avian tuberculosis.

Chickens, inoculated with the human and bovine forms of the bacilli and killed 60 to 90 days later, are free from the morbid changes so characteristic of tuberculosis when the disease is induced experimentally in susceptible animals. Although an occasional chicken becomes extremely thin and may even die a few weeks after receiving the inoculum, significant evidence of a tuberculous infection is not disclosed by the necropsy findings.

In a previous communication (4) it was shown that the introduction of human and bovine tubercle bacilli into the substance of the cerebrum of chickens induced definitely characteristic morphological changes of a tuberculous character. The lesions remained localized and progressed

[1] From the Institute of Experimental Medicine, the Mayo Clinic, Rochester, Minnesota. Received for publication, April 4, 1933.

slowly. Since, by a relatively simple procedure, it was possible to establish lesions in the tissues of chickens by the introduction of human and bovine tubercle bacilli, it seemed desirable to extend the observations in order that a study might be made of the anatomical and allergic manifestations that might be invoked when the organisms were introduced intracerebrally as well as by other routes.

Briefly the following objectives were sought: (1) knowledge concerning the allergic state at different intervals over a long period, as determined by the intracutaneous injection of tuberculin; (2) evidence of tuberculous infection at different intervals after exposure, as determined by bacillary culture, histological and animal-inoculation procedures; and (3) information regarding the fixity of the pathogenicity of human and bovine tubercle bacilli by successive passages through chickens, utilizing the intracerebral method of infection.

METHODS

The chickens were all adults of the white Leghorn breed raised for the laboratory. Most of those used were hens. All chickens were more than a year old; the majority were between one and two years. Before being accepted for the experiment each chicken was given intracutaneous injections of mammalian[2] and avian tuberculins of standard dilution (Old Tuberculin, 50 per cent). The injections were made into pendulous portions of the wattles.

The cultures represented original strains which I have previously isolated from spontaneously infected material. They were as follows:

Strain 744: Bovine; obtained in March, 1930, from a tuberculous lesion of a bronchial lymph node of a cow reacting to tuberculin. Typed by the inoculation of rabbits, guinea pigs and chickens as *Mycobacterium tuberculosis bovis.*
Strain 839: Human; isolated in September, 1930, from the sputum of a human being affected with pulmonary tuberculosis. Typed by the inoculation of rabbits, guinea pigs and chickens as *Mycobacterium tuberculosis hominis.*
Strain 849: Secured in September, 1931, from a tuberculous lesion of a mesenteric lymph node of a cow which had reacted positively to the tuberculin test. Typed by the inoculation of rabbits, guinea pigs, and chickens as *Mycobacterium tuberculosis bovis.*

Cultures of the respective strains of bacteria which were grown on Herrold's egg-yolk-agar medium for approximately four weeks at 37°C.

[2] Prepared as Koch's Old Tuberculin from human or bovine tubercle bacilli.

TABLE 1

*Summary of results following the injection of chickens with tuberculin after inoculation with bovine strain of the organism of tuberculosis, 849, in pure culture and in tissue emulsions of chickens in which lesions had developed**

CHICKEN	SOURCE AND CHARACTER OF INOCULATION	ROUTE OF INOCULATION	TESTS																DAYS BEFORE DEATH
			1st		2nd		3rd		4th		5th		6th		7th		8th		
			A†	M	A†	M	A†	M	A†	M	A†	M	A†	M	A†	M	A†	M	
1	Culture suspension	Intracerebral	−	−	+4	+4	−	−	−	+1									271 killed
2	Culture suspension	Intracerebral																	20 died
3	Culture suspension	Intravenous	−	+1	−	+1	−	−	−	−									271 killed
4	Brain emulsion of chicken 2	Intracerebral	−	−	−	−													53 killed
5	Brain emulsion of chicken 2	Intracerebral	−	−															53 killed
6	Brain emulsion of chicken 4	Intracerebral	−	−	−	−	−	−	−	−	−	−	−	−					413 killed
7	Brain emulsion of chicken 4	Intracerebral																	40 killed
8	Brain emulsion of chicken 4	Intravenous	−	+3	−	+3	−	+4	−	+2	−	+4	−	+4	−	+1	−	+2	385 killed
9	Brain emulsion of chicken 4	Intravenous	−	+1	−	+3	−	+4	−	−	−	+1	−	+3	−	+1			325 died
10	Brain emulsion of chicken 7	Intracerebral	−	+2	+2	+3	−	+1	−	+4	−	+3	−	+1	−	−	−	+4	345 killed
11	Brain emulsion of chicken 7	Intracerebral	−	−	−	−													44 killed
12	Brain emulsion of chicken 7	Intravenous	−	+2															51 died
13	Brain emulsion of chicken 7	Intravenous																	24 died
14	Brain emulsion of chicken 11	Intracerebral	−	−	−	+4	−	−	−	−	−	+1							296 killed
15	Brain emulsion of chicken 11	Intracerebral	−	−	−	+1	−	−	−	+2	−	+2	−	+1					296 killed
16	Brain emulsion of chicken 11	Intravenous	−	+3	−	−	−	−	−	+1	−	+2	−	+1	−	+2			296 killed
17	Brain emulsion of chicken 11	Intravenous	−	+2	−	−	−	−											127 died
18	Spleen emulsion of chicken 12	Intravenous	−	+1															80 died
19	Spleen emulsion of chicken 12	Intravenous	−	−	−	−	−	−	−	−	−	−							291 killed
20	Spleen emulsion of chicken 16	Intravenous	−	−															68 died
21	Spleen emulsion of chicken 16	Intravenous	−	−															68 killed
22	Spleen emulsion of chicken 12	Intravenous	−	−															68 killed

* The degree of the local allergic reaction is indicated by the following symbols: +1, small but definite reaction; +4, marked oedematous swelling of entire wattle; +2 and +3, reactions occupy the intermediate positions; −, negative result.

† A, avian tuberculin; M, mammalian tuberculin.

were used to prepare suspensions for the respective inoculations. The suspensions were equal in turbidity to tube number 1 of the McFarland nephelometer, and were thoroughly agitated before using in order to dissipate as many bacterial clumps as possible.

TABLE 2

Resultant infections which occurred in chickens 1 to 22 inclusive as determined by cultures, the presence of lesions and by the inoculation of guinea pigs

CHICKEN	CULTURE			LESIONS	GUINEA PIGS	
	Brain	Spleen	Liver		Inoculum	Results
1	0*	0	0	No lesions†	Not injected	
2	+	0	0	Brain lesions, extensive	Not injected	
3	0	0	0	No lesions	Not injected	
4	+	0	0	Brain lesions	Brain	Tuberculosis
5	+	0	0	Brain lesion	Not injected	
6	−	0	0	Brain lesion	Brain	Negative (both guinea pigs)
7	+	0	0	Brain lesions	Not injected	
8	0	−	0	Possible splenic lesions	Spleen	Failure‡
9	0	0	0	No lesions	Not injected	
10	−	−	0	Brain lesions	Brain and spleen	No tuberculosis
11	+	0	0	Brain lesions	Not injected	
12	0	−	−	No lesions	Spleen	Tuberculosis
13	0	0	0	Lesions in liver and spleen	Not injected	
14	−	−	−	Brain lesions	Brain, liver and spleen	Negative
15	−	0	0	Brain lesions	Brain and spleen	Negative
16	0	−	0	Splenic lesions	Spleen	Negative
17	0	0	0	No lesions	Not injected	
18	0	0	0	No lesions	Not injected	
19	0	−	0	No lesions	Spleen	Negative
20	0	0	0	No lesions	Not injected	
21	0	0	0	No lesions	Not injected	
22	0	0	0	No lesions	Not injected	

* Indicates that cultures were not attempted.

† The head of this chicken was inadvertently discarded when the animal was killed and whether the brain contained lesions of tuberculosis is problematical.

‡ Both guinea pigs died of pneumonia approximately two weeks after inoculation.

EXPERIMENT 1

Using a bacterial suspension prepared from bovine strain 849, a group of three chickens was inoculated, two intracerebrally and one intrave-

nously. In case significant lesions developed in any of these chickens it was the intention to inoculate others in succession with an inoculum prepared from the affected tissue. This procedure was to be followed successively through the different chickens in which lesions developed in sequence. A total of 22 chickens was inoculated, with results as summarized in tables 1 and 2. Usually four weeks after exposure to infection the respective chickens were subjected to tests of mammalian and avian tuberculin of

FIG. 1. (Chicken 1). Inoculated intracerebrally with suspension of the organism of bovine tuberculosis, strain 849. Forty-six days later reactions were negative following intracutaneous injections of mammalian and avian tuberculin. Marked reaction followed intracutaneous tuberculin test 161 days subsequent to infection. The right wattle was injected with avian tuberculin and the left with mammalian tuberculin.

standard 50 per cent dilution injected intracutaneously in amounts of approximately 0.03 cc. The interval between the subsequent tuberculin tests was somewhat variable, and from thirty to sixty days. Only definitely oedematous swellings were considered positive reactions, which were occasionally profound.

Many of the chickens that were killed during the first ten weeks after receiving the infectious material were near death, and were killed in order that suitable tissue could be secured for subsequent procedures.

By the successive inoculation of infectious material, bacteria from a culture of bovine tubercle bacilli or their descendants were passed through chickens for five generations. From these results there is no evidence of an acquired adaptability which enhanced the virulence of the organisms for chickens. It seems significant, however, that a marked allergic condition developed in many chickens which in some instances persisted for months, although subsequent studies failed to disclose anatomical evidence of a tuberculous infection. The converse was likewise of interest, in that many of the chickens that failed to give a positive response to the injection of tuberculin possessed definite lesions of tuberculosis from which virulent bacilli could be cultured. For the most part, these were chickens on which necropsy was performed in the first few weeks after exposure to infection.

In only two instances did a reaction occur following the injection of tuberculin prepared from the avian form of the organism (figure 1). This occurred in chickens 1 and 10. The reaction to the avian tuberculin was observed only once in each chicken, susbsequent tests being negative.

EXPERIMENT 2

Bongert, in reviewing a contribution by Pallaske-Eber, remarked that he had been able to infect chickens with bovine tubercle bacilli introduced into the upper part of the respiratory tract, and after several passages obtained transmutation from the human and bovine to the avian form of the organism. Bongert's results made it desirable to attempt a similar experiment.

Seven chickens were selected, and four were given intratracheal injections of 0.5 cc. bacterial suspension of human tubercle bacilli, strain 839. The remaining three chickens were given intravenous injections, each receiving 1 cc. of the bacterial suspension used to inoculate the first four. Thirty days after exposure they were inoculated intracutaneously simultaneously with mammalian and avian tuberculins of the standard dilution (Old Tuberculin, 50 per cent). Subsequent tuberculin tests were done, as shown in table 3.

Another group of 6 chickens was selected for additional observations following the intratracheal injection of a bacterial suspension prepared from bovine strain 744. The dosage used was 0.5 cc. of the suspension for each of the 4 chickens that were inoculated by way of the respiratory tract, whereas the two chickens inoculated intravenously each received 1 cc.

Fifty-seven days after receiving the bacterial suspension, swabbings deep into the throats were made from the 4 chickens that were given intratracheal injections of bovine strain 744. This was done to determine if the bacteria were being eliminated by the respiratory passages, which would be a reasonable assumption if progressive lesions of tuberculosis had become established in the pulmonary tissues. The cotton swabs were thoroughly washed in sterile saline solution and the fluid was divided into two equal portions and injected into two guinea pigs, which were killed for necropsy eight weeks later. With the exception of chicken 30 all were permitted to live for a period of 251 days before being killed.

TABLE 3

Results following the injection into the trachea of four chickens and into the wing-vein of three others of bacilli of tuberculosis derived from a human being

CHICKEN	ROUTE OF INOCULATION	TESTS										DAYS BEFORE DEATH	LESIONS OF TUBERCULOSIS
		30*		42*		49*		36*		33*			
		A†	M	A†	M	A†	M	A†	M	A†	M		
23	Intratracheal	+1	+3	−	+1							118 died	Neoplasia, not tuberculous
24	Intratracheal	+3	+3	−	+3	−	S‡	−	−	−	−	202 killed	No lesions
25	Intratracheal	−	+3	−	−	−	−	−	−	−	−	210 killed	No lesions
26	Intratracheal	S	+3	−	+1	−	+1	−	−	−	+1	210 killed	No lesions
27	Intravenous	+1	+2	−	+2	−	+3	−	−	−	−	210 killed	No lesions
28	Intravenous	+1	+3	−	−	−	−	−	−	−	−	210 killed	No lesions
29	Intravenous	−	−	−	+2	−	−	−	−	−	−	210 killed	No lesions

* Days after exposure to bacterial inoculation and between subsequent tuberculin tests.
† A, avian tuberculin; M, mammalian tuberculin.
‡ Slight reaction.

Chicken 30 was killed for necropsy seventy-two days after receiving the bacterial inoculum. The tuberculin tests were done with tuberculin of the dilution usually employed in making the intracutaneous tuberculin test in chickens (Old Tuberculin, 50 per cent). A summary of this part of the experiment is given in table 4.

From the results obtained in experiment 2, there is nothing to warrant the belief that human and bovine tubercle bacilli will assume the characteristics of the avian form of the organism as a consequence of a pulmonary residence in chickens. The lungs, livers and spleens of all of these chickens failed to reveal evidence of tuberculous infection either grossly or microscopically. In none of the guinea pigs inoculated with

the washings prepared from the throat swabs did tuberculosis develop. It is true, however, that in all of the chickens a transitory allergic state developed, which, although markedly detected by tuberculin prepared from the bacilli of mammalian tuberculosis, did, in a few instances, become definitely evident after the injection of avian tuberculin. In 2 chickens the degree of the allergic reaction, as measured by the oedematous swelling of the wattles, was recorded for each as +3. This would indicate that under certain conditions so-called cross reactions to tuberculin are likely to occur, and depreciates the value of the view that a positive reaction following an injection by avian tuberculin is indicative of an infection by the organism of avian tuberculosis.

TABLE 4

Summary of results obtained following the intratracheal and intravenous inoculation of chickens with the bacilli of bovine tuberculosis

CHICKEN	ROUTE OF INOCULATION	TESTS								THROAT SWABS	LESIONS OF TUBERCULOSIS
		32*		49*		44*		52*			
		A†	M	A†	M	A†	M	A†	M		
30	Intratracheal	+3	+3	−	−					Negative	No lesions
31	Intratracheal	−	+3	−	+2	−	S‡	−	S‡	Negative	No lesions
32	Intratracheal	−	+3	−	−	−	−	−	−	Negative	No lesions
33	Intratracheal	−	+2	−	+1	−	S‡	−	S‡	Negative	No lesions
34	Intravenous	−	−	−	+3	−	−	−	−		No lesions
35	Intravenous	−	+2	−	−	−	−	−	−		No lesions

* Days after injection of the bacterial suspension and between subsequent tuberculin tests.

† A, avian tuberculin; M, mammalian tuberculin.

‡ Slightly positive reaction.

EXPERIMENT 3

A study was made to determine if greatly reduced concentrations of tuberculin would elicit evidence of an allergic state in chickens injected with human and bovine tubercle bacilli. Compared to the amount of Old Tuberculin usually injected for diagnostic purposes in cattle and in human beings, the dosage originally recommended by Van Es and Schalk (13) for the diagnosis of tuberculosis of chickens seems tremendous.

Five chickens were inoculated intravenously with a bacterial suspension prepared from a culture of strain 839 of human origin, and two chickens were inoculated in the same manner with a suspension prepared from a culture of the organism of bovine tuberculosis, strain 744. The

TABLE 5

Sensitivity of chickens to human, bovine and avian tuberculin of variable concentrations after intravenous inoculation with organisms of human and bovine tuberculosis

CHICKEN	INOCULUM	DILUTION OF TUBERCULIN*	TESTS												DAYS BEFORE DEATH	LESIONS OF TUBERCULOSIS AND RESULTS OF GUINEA-PIG INOCULATIONS
			14†		14†		30†		30†		20†		27†			
			A‡	M	A‡	M	A‡	M	A‡	M	A‡	M	A‡	M		
36	Bovine strain 744	Dilution II	−	+3											18 killed	Lesions in liver and spleen; liver and spleen infectious for guinea pigs
37	Bovine strain 744	Regular	−	+2	−	+2	−	+2	−	−	−	−	−	−	187 killed	No lesions; spleen not infectious for guinea pigs
38	Human strain 839	Dilution II	−	−	−	+1	−	+1	−	+3	−	−	+1	+1	187 killed	No lesions; spleen not infectious for guinea pigs
39	Human strain 839	Dilution I	−	+3											18 killed	Splenic lesions; liver and spleen infectious for guinea pigs
40	Human strain 839	Dilution I	−	+1	−	+3									32 killed	Splenic lesions; liver and spleen not infectious for guinea pigs
41	Human strain 839	Regular	−	+1	−	−	−	+1	−	−	−	+4	−	−	187 killed	Splenic lesions; spleen not infectious for guinea pigs
42	Human strain 839	Regular	−	+2	−	+3									32 killed	Splenic lesions; spleen infectious for guinea pigs; liver not infectious

* The dilutions of tuberculin were as follows: Regular, containing in each cubic centimetre 0.5 cc. of Old Tuberculin; dilution I, containing in each cubic centimetre 0.01 cc. Old Tuberculin; dilution II, containing in each cubic centimetre 0.001 cc. of Old Tuberculin.

† Days after injection of the bacterial suspension and between subsequent tuberculin tests.

‡ A, avian tuberculin; M, mammalian tuberculin.

dosage for each animal was 0.5 cc. Two weeks after the infectious material was introduced, the chickens were inoculated with tuberculin of varying concentration (table 5). The respective chickens were killed at different periods, and the presence of tuberculous infection was determined by macroscopic or microscopic lesions, and by the injection into guinea pigs of emulsions prepared from the liver or spleen, or both, of the different individuals. Two guinea pigs were given injections of each emulsion.

The observations in experiment 3 (table 5) would indicate that the allergic state induced in chickens exposed to virulent bacteria of human and bovine tuberculosis may be evoked by tuberculin in extremely dilute concentrations. The frequency of positive reactions elicited by this tuberculin and the failure of avian tuberculin injected simultaneously to provoke similar results suggest a significant relationship between the provocative bacterium and the character of the agent used to evoke the allergic state. One should be cautious, however, in reaching conclusions from these data, since the nonspecificity of the tuberculin reaction has frequently been observed.

It is also evident from the data presented in experiment 3 that there is an apparent correlation between the duration of the infection, the intensity of the allergic phenomena and the persistence of pathogenicity on the part of the infecting bacteria. Sensitivity to tuberculin and the presence of bacteria in a viable, virulent state were most likely to occur when the chickens were killed during the first few weeks of the experiment. After a prolonged period the infection appears to become lessened, and is eventually eliminated. This can be well demonstrated by a study of the histopathology of lesions in chickens in which infection has been established.[3]

EXPERIMENT 4

The previous observations clearly demonstrated the ability of the tissues of the chicken to cope successfully with virulent organisms of human and bovine tuberculosis, even though the organism was introduced in large numbers directly into the blood-stream or into the pulmonary passages. Most of the observations were based on chickens which had been exposed to infection many weeks before being killed. It seemed pertinent, therefore, to determine something concerning the fate of the infecting

[3] The histopathology induced in chickens infected with human and bovine tubercle bacilli is the subject of a separate communication (*Amer. Rev. Tuberc., 1934, xxix, 415*).

bacteria at intervals up to one week following their introduction into the body. With this in mind, 6 chickens were each given intravenous injections of 0.5 cc. bacterial suspension of human strain 839. They were then killed at intervals; one after seven minutes, one after thirty minutes, one after one hour, one after six hours, one after twenty-four hours and one after seven days.

At necropsy half of the spleen and a small portion of the liver were secured aseptically, and, after being thoroughly emulsified in physiological solution of sodium chloride, a 1-cc. portion of each organ emulsion was used for culture on the egg-yolk-agar medium of Herrold. The

TABLE 6

Summary of the results obtained when chickens that had been inoculated intravenously with virulent bacilli of human tuberculosis were killed at intervals of seven minutes to seven days subsequent to inoculation

CHICKEN	INTERVAL AFTER INJECTION BEFORE DEATH	CULTURE OF ORGANISM		TUBERCULOSIS IN GUINEA PIGS INOCULATED WITH EMULSIONS PREPARED FROM LIVER AND SPLEEN OF RESPECTIVE CHICKENS	
		Liver	Spleen	Liver	Spleen
43	7 minutes	−	−	Extensive lesions	Extensive lesions
44	30 minutes	+	+	Extensive lesions	Extensive lesions
45	1 hour	+	+	Negative	Lesions few but definite
46	6 hours	+	−	Lesions limited to 1 precrural lymph node	Negative
47	24 hours	+	−	Extensive lesions	Failure*
48	7 days	−	+	Few lesions in spleen; liver normal; 1 precrural lymph node extensively affected	Extensive lesions

* Died two weeks after inoculation.

remainder of the spleen and portions of the liver and parts of both lungs were preserved for histological study. Guinea pigs were given a subcutaneous injection of 1 cc. each, of the respective organ emulsions used to make cultures. After a period of eight weeks the guinea pigs still living were killed for necropsy (table 6).

None of the tissues of the 6 chickens in this series revealed the slightest evidence of infection with tuberculosis, although the presence in the liver or spleen of bacilli of sufficient virulence to induce well-defined characteristic lesions in guinea pigs was proved.

It is evident from this experiment that all of the bacteria injected were not immediately destroyed. Apparently it requires longer than

seven days for bacteria of the kind used to provoke lesions in the tissues of chickens and for the defensive factors of the chicken to affect the bacterium sufficiently adversely to cause its incapacitation.

The results obtained in chicken 45, which was killed one hour after receiving the bacterial suspension, are of some interest as were those of chicken 43. In the former, although cultures of organisms of tuberculosis were secured from emulsions of the liver and spleen, the emulsion of the liver failed to incite lesions of tuberculosis in a guinea pig and that of the spleen produced mild lesions. Why cultures of acid-fast bacteria were not obtained from the emulsions of liver and spleen of chicken 43, although in guinea pigs inoculated with portions of the same material extensive tuberculous lesions developed, is difficult to understand. Perhaps the inclusion of the infectious organisms within certain phagocytic cells from which they were later released within the tissues of the guinea pig might constitute a partial explanation. However, it is evident that phagocytosis, if it obtained, did not prevent the securing of cultures from the liver and spleen of chickens 44 and 45.

The data pertaining to experiment 4 are too meagre to justify other than certain general conclusions. If certain specific facts are to be elicited it would seem desirable that this experiment be repeated and perhaps extended.

COMMENT

The observations constituting the basis of this study confirm the conclusions of other observers whose results led them to believe that the domestic hen is markedly refractory to bacteria of human and bovine tuberculosis. The reports of Martin, Straus and Wurtz, Maffucci, Cadiot, Gilbert and Roger (2), Zwick, Moore, de Jong, Van Es and Schalk (14), Beller and Henninger, and others provide sufficient data to warrant the conclusion that chickens are not susceptible to the bacteria of human and bovine tuberculosis in the accepted sense of the term. Even when definitely tuberculous foci are established in the brain as a consequence of intracerebral exposure to the organism, the infection is usually limited in extent and seldom promotes dissemination of the disease to such organs as the lungs, liver and spleen.

It is true that the resistance of the tissues of chickens to infection with organisms of human and bovine tubercle bacilli is not absolute. In many chickens a definitely morbid process is established. This apparently is not demonstrable morphologically until two to three weeks after the or-

ganisms are introduced. The lesions are generally atrophic in appearance unless they are examined in the earlier formative stage. The infectious process is finally brought under complete submission by the protective mechanism of the body, and anatomical evidence of the disease disappears usually within 60 to 90 days. Animals examined after the lapse of six months to one year after exposure to the organism are almost always devoid of lesions. In those infrequent instances in which tuberculous lesions persist for a prolonged period, they are generally, if not always, free from viable or virulent acid-fast bacteria. In lesions of long duration, it is not uncommon to find bacterial débris from which viable bacteria cannot be obtained by either culture methods or by the inoculation of animals.

My failure to consummate a definite transmutation of the bacteria of human and bovine tuberculosis to organisms with enhanced pathogenicity for chickens does not invalidate the hypothesis that such a transition is possible. It does emphasize the stability of these bacteria, and makes it evident that marked alterations in their biological behavior are difficult to achieve.

That the exposure of chickens to organisms of tuberculosis of human and bovine origin would result in a sensitivity to tuberculin was not unexpected. The majority of the positive reactions obtained was sufficiently well defined to be characteristic of this well-known diagnostic procedure.

For the most part, there seemed to be a significant relationship between the allergic state as evoked by the injection of tuberculin and the presence within the tissues of viable and virulent bacteria. Although the data are not entirely convincing, the evidence suggests that a tuberculous lesion, when provoked in chickens by organisms of tuberculosis of human or bovine orgin, loses its relationship to allergic phenomena unless the bacteria responsible for the lesion continue in a viable and virulent state. In other words, the presence of the cytological structure known as the tubercle will not alone incite or continue a sensitization to tuberculin. There must be present a bacillus of tuberculosis which has retained its pathogenicity.

SUMMARY AND CONCLUSIONS

For the purpose of obtaining additional information concerning the susceptibility of chickens to bacilli of human and bovine tuberculosis, a series of 48 adult chickens was subjected to infection. Virulent organisms

of tuberculosis, of human and bovine origin, were used to inoculate the animals as follows: by intravenous injection, 30 chickens; by intracerebral injection, 10 chickens; and by intratracheal injection, 8 chickens. After exposure to infection, chickens were frequently given injections of avian and mammalian tuberculin for the purpose of disclosing the existence of an allergic state.

The chickens were killed for necropsy at different periods up to 413 days after receiving the infective bacteria. Utilizing the intracerebral method of inoculation, a strain of bacteria of tuberculosis of bovine origin was passed successively in sequence through chickens for five generations. Data obtained seem to warrant the following conclusions:

1. Chickens are extremely resistant to the bacteria of human and bovine tuberculosis.

2. Tuberculous lesions can be induced by the intracerebral method of inoculation. Lesions that developed as a consequence of the introduction of large numbers of the bacilli intravenously are never progressive, and tend to disappear after a relatively short time.

3. Organisms of human and bovine tuberculosis present in the lesions in the tissues of chickens soon become nonviable and disintegrate.

4. It is improbable that a malignant, progressive tuberculous infection can be induced in chickens by the organisms of tuberculosis that are typically bovine or human in type.

5. The exposure of chickens to organisms of tuberculosis of human or bovine origin provokes an allergic state which can be demonstrated by the intracutaneous injection of mammalian tuberculin. Occasionally a chicken given injections of these forms of bacteria will give a positive allergic reaction following the injection of avian tuberculin.

6. Residence of the organisms of human and bovine tuberculosis within the tissues of chickens failed to increase their adaptability for an avian environment or to enhance their virulence.

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PATHOLOGICAL CHANGES INDUCED IN CHICKENS BY HUMAN AND BOVINE TUBERCLE BACILLI[1]

WILLIAM H. FELDMAN

In a previous paper I recorded observations on results following attempts to establish a tuberculous infection in chickens by inoculation with virulent human and bovine tubercle bacilli. The studies revealed a definite resistance of chickens to bacteria of this character, even though the organisms were injected in large numbers and by the most vulnerable portals of entry. Although in none of the 48 chickens used in the previous study did progressive, malignant tuberculous lesions occur, in many of the chickens there were definite morphological changes of characteristic tubercle appearance. These changes were most noticeable in the chickens that were inoculated intracerebrally, although they could be recognized in many of those inoculated intravenously, provided tissues were examined from chickens that died or were killed after the second or third week following inoculation and before the disappearance of the lesions, an event that probably occurs in most instances sixty to ninety days after exposure.

I shall consider here the histo-pathology of the tissue reactions in the various organs in which demonstrable infection occurred. Most of the tissues secured for study were obtained immediately after death and fixed in a neutral 10 per cent solution of formaldehyde. Paraffin sections were prepared and stained by haematoxylin-eosin and others by carbol-fuchsin by a method previously described (2). The only organs in which lesions of tuberculous character were found were the brain, liver and spleen.

BRAIN

The character and extent of the morphological alterations varied with the duration of the disease. The earliest lesions of the brain studied were those of a chicken inoculated intracerebrally with a suspension of bovine tubercle bacilli twenty days before death. That the disease in

[1] From the Institute of Experimental Medicine, The Mayo Clinic, Rochester, Minnesota. Received for publication April 4, 1933.

this instance was aggravated and progressive was evident from the fact that the chicken died as a consequence of the infection.

The lesions of longest duration were those found in the brain of a chicken inoculated 413 days prior to being killed. The duration of the disease in the other brains studied was 46 days, 44 days, 53 days, 56 days, 136 days, 292 days, 296 days, and 345 days.

Although the infecting bacteria were placed in the depths of the cerebral substance, meningeal involvement was observed in several instances. This was usually limited to the hemisphere of the cerebrum receiving the inoculum, although occasionally the meninges of both cerebral hemispheres were affected. The morbid process apparently began in the perivascular tissues of the pia mater and was characterized by the occurrence of small, focal collections of monocytic or epithelioid cells surrounded by many lymphocytes which extended under and into the pia mater in a continuous spread. Occasionally a well-defined nodular accumulation of epithelioid cells was to be seen projecting outward from the surface of the cerebellum. These were always under the pia mater and invested with a peripheral zone of lymphoid cells (figure 1). Although lesions were sometimes seen deep in the sulci of the cerebellum, none was found in the substance of this part of the brain. A few foci of infection were seen infrequently around the blood-vessels of the deep longitudinal fissure separating the cerebral hemispheres. The lesions of this intracerebral zone were often numerous and extensive in chickens in which the disease was prolonged.

Generally, two forms of the morbid process occurred in the cerebral tissue. One was a large diffuse or conglomerate collection of epithelioid tubercles with a central area of caseation-necrosis and the other was characterized by the formation of small, discrete miliary tubercles which appeared to have their inception in the tissues immediately adjacent to the vascular channels. The large conglomerate lesions were evidently the result of the fusion of several adjacent smaller tubercles. A perivascular infiltration of monocytic and lymphocytic cells was strikingly evident in association with many of the cerebral infections (figure 2). This feature extended peripherally from the larger and well-established tuberculous lesions.

In the formative stage a typical tubercle, which must be considered the anatomical unit of the morbid process, consisted of a focal collection of monocytic cells which early revealed a tendency to become epithelioid, and of relatively few lymphocytes. With the development of the struc-

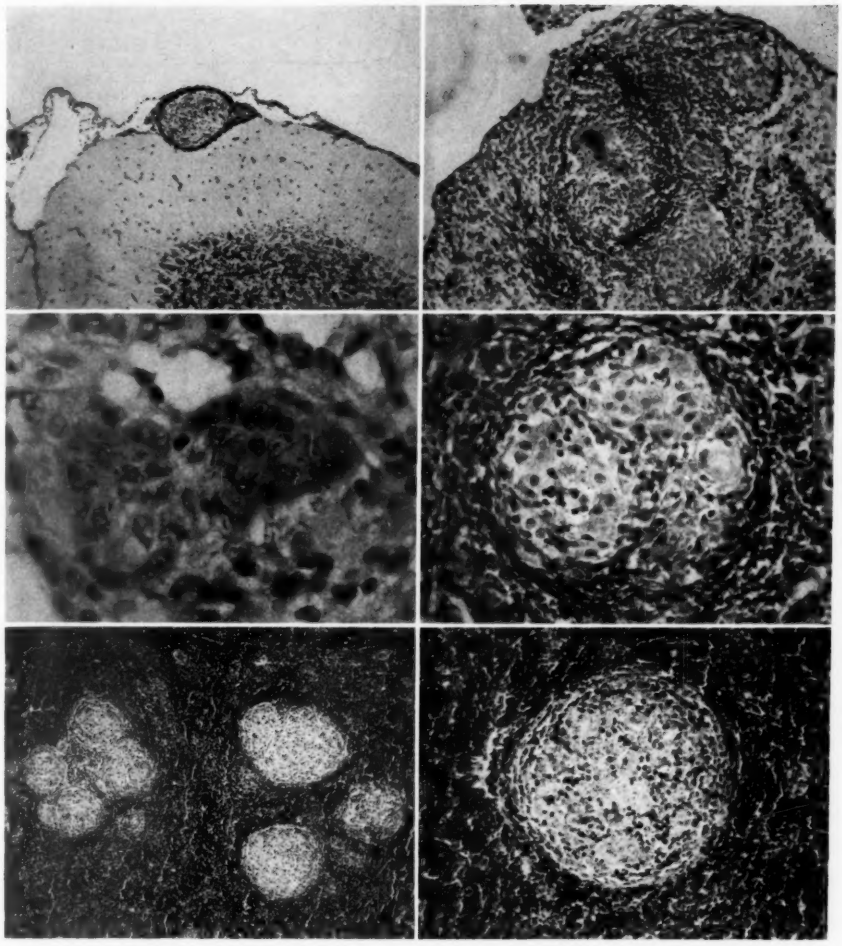

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 1. CHARACTERISTIC TUBERCLE AT THE SURFACE OF THE CEREBELLUM OF A CHICKEN WHICH DIED 56 DAYS AFTER RECEIVING AN INTRACEREBRAL INJECTION OF HUMAN TUBERCLE BACILLI. (× 50)

FIG. 2. LESIONS IN THE BRAIN OF A CHICKEN THAT WAS KILLED 40 DAYS AFTER RECEIVING AN INTRACEREBRAL INJECTION OF BOVINE TUBERCLE BACILLI. ONE LARGE GIANT CELL IS PRESENT. (× 85)

FIG. 3. NUMEROUS ACID-FAST BACILLARY FORMS WITHIN COLLECTIONS OF EPITHELIOID CELLS IN THE BRAIN OF A CHICKEN WHICH DIED 20 DAYS SUBSEQUENT TO INTRACEREBRAL INFECTION BY BOVINE TUBERCLE BACILLI. (× 550)

FIG. 4. TUBERCLE IN THE LIVER OF A CHICKEN INOCULATED WITH A SUSPENSION OF BOVINE TUBERCLE BACILLI 18 DAYS PREVIOUS TO BEING KILLED

Acid-fast bacillary forms were present among the epithelioid cells of the lesion, and an emulsion of a portion of the same liver produced tuberculosis in a guinea pig (see fig. 5). (× 242)

FIG. 5. NUMEROUS TUBERCLES IN THE SPLEEN OF A CHICKEN KILLED 18 DAYS AFTER RECEIVING AN INTRAVENOUS INJECTION OF BOVINE TUBERCLE BACILLI

An emulsion prepared from a portion of this spleen induced tuberculous infection in guinea pigs (see fig. 4). (× 60)

FIG. 6. SOLITARY TUBERCLE IN THE SPLEEN OF A CHICKEN KILLED 18 DAYS AFTER INTRAVENOUS INJECTION OF BOVINE TUBERCLE BACILLI. (× 142)

ture the central collection of epithelioid cells was gradually extended until these rather large, somewhat clear, cells predominated. During the first few weeks after the establishment of the collections of epithelioid cells, many morphologically intact acid-fast bacillary forms were to be seen (figure 3). These gradually diminished in number, and it was unusual to discern a typical acid-fast bacterium in lesions of eight to ten weeks' duration. Finally, as the acid-fast bacilli disappeared, there could be seen variable amounts of a fragmented acid-fast substance that persisted as inclusions within the cytoplasm of the epithelioid cells. This substance was frequently seen as granulated clusters. Whether it has a relationship to the acid-fast bacteria that previously occupied the epithelioid structures is problematical. Lesions containing such fragmented material and no typical acid-fast bacillary forms always failed to infect guinea pigs and never yielded a culture of tubercle bacilli.

After the epithelioid tubercle became definitely established there frequently occurred a tremendous infiltration of lymphocytic cells which usually extended around the entire periphery of the epithelioid structure. The lymphoid cells eventually diminished in number and persisted in only moderate quantities in the lesions of considerable duration.

As the process continued significant changes occurred. With the passing of the progressive stage of the morbid process and the incapacitation of the provocative agent, the collection of epithelioid cells frequently became vacuolated and eventually atrophic. A surrounding fibrosis became apparent, which gradually encroached on the retrogressive tuberculous structure which could be expected to disappear eventually. If there was a large amount of fibrous tissue it eventually became contracted, and hyalinization was frequently observed. A few lymphocytic cells usually persisted. Small, solitary tubercles apparently disappeared after an atrophic existence, and left no trace of their previous occupancy.

In the larger lesions, where extensive necrosis had occurred, the epithelioid cells in the zone of contact with the necrobiotic process assumed a characteristic appearance. The cells were arranged with the longitudinal axis at right angles to the periphery of the lesion and the respective cells were thin, drawn out, and fibroblastic. Multinucleated masses or giant cells were occasionally present. It was difficult to correlate the occurrence of giant cells with the duration of the disease, but their presence did seem to bear a relationship to the retrogressive or inhibitory process. They were not seen in those lesions that were aggressively active, whereas those which contained them were in or approaching a quiescent state.

Mineral salts must be deposited but rarely in lesions of the brains of chickens induced by the human and bovine organisms of tuberculosis. It has been observed once in the material I have studied and was small in amount.

It seems àpropos to reiterate my previous opinion (1) that regardless of the source of the provocative agent there is a consistent similarity in the cellular response of chickens exposed to the bacteria of tuberculosis. The lesions induced by the human and bovine tubercle bacilli were essentially the same. In fact, they resembled each other so closely that differentiation was impossible on morphological criteria.

LIVER

With one exception the relatively few instances in which specific lesions were produced in the liver by human and bovine tubercle bacilli developed as a consequence of an intravenous exposure. A few lesions were present in the liver of a chicken that had been inoculated intracerebrally 271 days prior to death with a culture of the bovine bacillus. None of the material studied contained lesions of sufficient size to be seen by the unaided eye.

The morphology of the lesions in the liver was essentially the same as the cellular response to the same bacteria in the brain. The tubercles, however, were less frequently observed as conglomerate units, appearing usually as single, discrete foci. The anatomical distribution of the lesions was without significance and was more promiscuous.

The histology of a typical lesion reveals a more or less spherical collection of closely arranged epithelioid cells which seem fairly resistant to necrobiosis (figure 4). Peripherally there are present variable numbers of monocytes and lymphoid cells, the latter becoming more numerous as the duration of the lesion is extended. Lesions examined in their early formative stages will disclose the presence of acid-fast bacillary forms within the cytoplasm of some of the epithelioid cells. In the material examined these have never been numerous. In the older lesions the bacteria disappear, and there remains in some of the tubercles acid-fast granular or particulate material of uncertain significance.

Unless the infection has been exceedingly formidable the tuberculous foci eventually become atrophic and disappear with a consequent restoration of the parenchymal structure. Since fibrosis is minimal in amount or absent, encapsulation is uncommon in lesions of this character. This circumstance seems to enhance the possibility of ultimate and

complete elimination of all anatomical evidence of infection. Epithelioid cells of tubercles in the later stages of their existence not infrequently revealed a structural disintegration. This was evident from the presence of vacuoles or spaces within the cytoplasm of many of the cells.

Even in those instances in which multiple lesions occur the functional derangement of the liver must be small. The individual foci are never large, and the only discernible effect on the adjacent hepatic cells is an atrophic compression of those in the immediate zone of contact.

The relatively small size of the respective tubercles and the disinclination of these structures to become encapsulated probably enable the collection of epithelioid cells to continue in a viable state longer than would be true otherwise, and may account for the few necrotic changes. In no instance in the material studied was calcification observed.

As was true of the lesions of the brain there was no demonstrable difference in the anatomical reactions to the human and bovine bacilli.

SPLEEN

In only one instance was involvement of the spleen sufficient to be seen without the aid of the microscope. The chicken had received an intravenous injection of an emulsion prepared from the tuberculous brain of another chicken. The chicken was killed 296 days subsequent to inoculation and, although the lesions were striking in appearance, the presence of a virulent bacterium could not be demonstrated by the inoculation of guinea pigs. Attempts to secure cultures from the splenic emulsion of this chicken also failed. The infecting organism was of bovine origin.

The lesions in the spleen of chickens provoked by the tubercle bacilli of human and of bovine types, like those of the brain and liver, were of a follicular nature. They had their inception in the tissues within the splenic corpuscles, and apparently in significant relation to the vascular channels. Although ordinarily only one tubercle was found in a given splenic corpuscle, it was not uncommon to observe several crowding the interior of the same structure and eventually producing a conglomerate unit (figure 5). The structure of an individual tubercle consisted of closely arranged packets of epithelioid cells and a few lymphocytes and granular leucocytes (figure 6). In those examined during the early period of their existence it was not unusual to find variable numbers of monocytic cells with an occasional form undergoing mitosis.

Encapsulation with a peripheral zone of fibroblastic tissue was not ob-

served even in the splenic lesions present in the chicken which was permitted to live 296 days after receiving the injection. In some of the tubercles, particularly those which had persisted for 150 days or more, central necrosis was evident. In the lesions examined the necrotic material in the interior of the tubercle resembled a coagulating rather than a caseous variety of necrosis. In lesions with a necrotic centre the intact epithelioid cells at the periphery revealed a marked tendency to fuse into irregular cytoplasmic masses suggestive of giant-cell formation.

Characteristic acid-fast rods were present in large numbers in many of the cells constituting the lesions in the earlier stages of the disease. The organisms seemed to diminish in number as the duration of the infection was prolonged. In the necrotic débris of the centre of a splenic lesion in a chicken that was killed 187 days after receiving the infectious inoculum an occasional acid-fast bacillus was to be seen, but an emulsion prepared from a portion of this spleen failed to infect guinea pigs.

In many of the lesions of considerable duration a large number of irregular globular masses of acid-fast material was to be seen in association with the intact epithelioid cells. This was particularly noticeable in the splenic lesions of a chicken killed 296 days after the infection was introduced. The nature of this material is obscure.

In no instance was calcification observed in the tuberculous lesions of the spleen, although some of them were large and filled with cellular detritus.

COMMENT

The pathological changes of tuberculous infection induced in chickens by human and bovine tubercle bacilli are those of a morbid process which has become established regardless of a profound biological resistance. With this in mind it is not surprising that the infection is usually self-limited and never widespread or malignant,—such as one would expect to develop in chickens exposed in a similar manner to avian tubercle bacilli. From the moment the bacteria enter the body of the chicken the environment is unfavorable, and, although the disease may progress to a limited degree in such tissues as the liver and spleen, the infection soon attains its maximal extent and enters a stage of gradual retrogression.

That infection should occur in the brain is not surprising, but even in this organ the course of the disease, when induced in chickens by human and bovine tubercle bacilli, is not always progressive, and eventual elimination of such an infection may sometimes occur.

Although the data are not entirely convincing, this study would suggest that the infection persisted longer in the spleen than in the liver, even though in the earlier stages of an infection introduced intravenously the primary distribution of the lesions was perhaps of equal degree in each of these organs.

A somewhat unique fact which has been obtained in these studies is that the bacilli responsible for the development of the lesions eventually become incapable of growth on culture media and are no longer able to produce lesions in guinea pigs:—this, regardless of the fact that the histological unit of the infection may persist, and contain typical acid-fast bacillary forms.

Although these studies have shown that under certain circumstances it is possible to incite specific tuberculous lesions in chickens by human and bovine tubercle bacilli, the character and extent of the disease produced are such as to confirm the general belief that the chicken possesses a profound natural resistance to infections of this type. In no instance did the organisms used produce a process comparable in its severity to that which results when chickens are exposed to the specific organism of avian tuberculosis. The value of chickens in determining the type of infection in human and bovine tuberculosis is in no way depreciated by the results of this study. It seems improbable that the organisms of human and bovine tuberculosis can ever be of aetiological significance in spontaneous tuberculosis of chickens.

SUMMARY AND CONCLUSIONS

Utilizing material that had been secured from a series of chickens exposed intracerebrally and intravenously to the human and bovine forms of the bacillus of tuberculosis, a histological study was made of the lesions that occurred in the brain, liver and spleen. The cytological reaction was that of a definitely tuberculous process, characterized by the occurrence of follicular accumulations of epithelioid cells. After a certain stage of progression the lesions became quiescent and tended eventually to disappear. In no instance did the infectious material initiate an aggressive malignant form of tuberculosis. From the observations recorded, the following conclusions are offered:

1. Chickens are extremely resistant to the organisms of human and bovine tuberculosis.

2. Definite and sometimes extensive tuberculous changes may follow the introduction of the bacteria of human and bovine tuberculosis into the substance of the brain.

3. When exposed intravenously to acid-fast bacilli derived from cases of human and bovine tuberculosis, a restricted tuberculous state not infrequently results in the liver and spleen.

4. After an initial period of progression the lesions produced in chickens by human and bovine tubercle bacilli become quiescent, and tend eventually to disappear.

5. A progressive, widely disseminated tuberculosis of chickens does not seem possible as a consequence of infection by human and bovine tubercle bacilli.

6. The tuberculous lesion in chickens inoculated with human and bovine bacilli is essentially a spherical collection of epithelioid cells with a peripheral accumulation of lymphocytes.

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CHILDHOOD-TYPE TUBERCULOSIS

As Revealed by the X-Ray[1, 2]

H. F. R. WATTS

Fifteen years ago, when many of us were in the Army and came under the influence and teaching of that veteran warrior of the old school in tuberculosis study, Col. George E. Bushnell, we came to believe, and in turn taught others, that childhood infection with tuberculosis imparted a certain immunity to the patient and afforded protection against the development of phthisis, and thus constituted an asset rather than a liability. That this theory was not entirely water-tight is now abundantly shown by the film files of every clinic in which may be seen in the films of the same patient the shadows of the old childhood type, or primary infection, and, in addition, those of adult phthisis, or reinfection tuberculosis as it is now called.

Fifteen years ago the refinements of X-ray diagnosis in pulmonary conditions had hardly begun, and I well remember the early scepticism of my old friend and teacher, the late Dr. Edward O. Otis, when the roentgenologist began to make chest diagnoses. In recent years the X-ray and the tuberculin test have thrown much light upon the problem of the genesis and natural history of tuberculosis of the lungs; and the family-folder feature of the diagnostic clinic, employing both of these agencies as a means of checking the incidence of the disease in the family contacts of a known case, has disclosed the existence of contact infections to an extent undreamed of fifteen years ago.

It is now generally accepted that a positive tuberculin skin reaction is indisputable evidence of tuberculous infection, whether or not this is capable of X-ray demonstration, and there are those who hold that, given a positive tuberculin reaction, infection being thereby established, the X-ray is then only useful to establish the absence or presence of phthisis or reinfection, and its extent if present.

[1] From the Tuberculosis Division of the Boston Health Department, Boston, Massachusetts.

[2] Read before the Eastern Section of the American Sanatorium Association, Grenloch, New Jersey, October 6, 1933.

The present author does not presume to expound the whole truth of the matter or to solve this or the many other problems in which this subject is involved, and which are knocking at our door for solution. The factors upon which the older theories were promulgated are many of them still sound. For instance: That, academically at least, as shown by animal experimentation, a degree of acquired immunity results from a primary infection. How much, if any, clinical importance may be attached to this is in doubt and in some dispute. Certain it is that in our experience we encounter large numbers of both children and adults whose X-ray films show the primary infection or childhood-type lesion who remain well, and whose lesions, as demonstrated by repeated X-ray examinations, remain unchanged for years and years, as against a minority of the same types who later develop phthisis. Inquiry usually reveals the fact that these comparatively few who later develop phthisis have been those who have been in constant intimate contact with cases of open phthisis.

That the old theory of relative immunity conferred by the primary infection should be entirely scrapped seems doubtful. We are forced, however, to a realization that the relative immunity is indeed relative, and by no means absolute.

A tabulation of X-ray findings, made in the tuberculosis diagnostic clinics of the Boston Health Department (now in operation for six years), for the twenty-nine months from May 1, 1931, to October 1, 1933, of 10,639 patients, of all ages, has suggested to the writer some speculations in addition to those which for years he has entertained with reference to the occurrence of childhood-type tuberculosis and to the influence which this may have upon the subsequent development of the adult type of the disease.

The purpose of this paper (which is a study of roentgen findings only) is to define what, in these clinics, is accepted as the roentgen evidence of the childhood-type tuberculosis as found in the chest, and to discuss pulmonary tuberculosis as seen in adults and children, under the three headings of (1) childhood type, (2) adult type, or phthisis, and (3) the combined form in which both types are seen to be present in the same patient.

The writer is aware that this presentation is but a one-sided view of a picture of childhood tuberculosis, the view presented by the X-ray films alone. It is not pretended that it is possible to establish by X-ray examination the absence of childhood-type tuberculous infection in all, or indeed, any of the cases in which it is not manifest. It has been the aim of this study to deal only with roentgenologically-demonstrable lesions, and to weigh all of the evidence in the same scales.

In order to conform to the prevailing classification, all patients of 17 years or more are called adults, and all under 17 are called children.

In this series of 10,639 patients who have been X-rayed during the past 29 months are many who have been repeatedly X-rayed and studied during the 6 years of the existence of the clinics. Between four or five thousand chest X-ray examinations are made each year.

The personnel of the X-ray service consists of one physician, one technician, and one stenographer, with the necessary nursing force.

Stereoscopic films at 6-feet target film distance are routine, except in very young children. Supplementary films in lateral and oblique positions are made as indicated. Fluoroscopy is used on selected cases only.

Of the 10,639 patients under consideration, 5,023 were adults and 5,616 were children. In the adult group, 380 (7½ per cent) showed roentgen evidence of childhood-type tuberculosis, uncomplicated by phthisis; 1,134, or 22½ per cent, showed roentgen evidence of phthisis, without evidence of the childhood type; while 92, or 2+ per cent, had both types of the disease. In the group of children, 511, or 9 per cent, were found to have childhood-type lesions, unaccompanied by adult phthisis; 16 had adult phthisis, unaccompanied by the childhood type; while 12 had both childhood and adult types.

The program of these clinics carries the mandate of seeking out or of excluding the presence of pulmonary tuberculosis in all comers.

The diagnosis of the childhood type of the disease has at all times engaged the particular attention of all the personnel of the clinic, and, early in the work, it became necessary to define the limits of this diagnosis in terms of roentgen shadows. Let it be stated at the outset that this procedure, at its best, still leaves much to be desired. In its mediocre state, and at its worst, it is misleading. Many instances of the childhood type of tuberculosis are still incapable of roentgenographic demonstration, because our methods (at best) are still too clumsy to reveal much that we should like to know. Uncalcified traceheobronchial, mediastinal and hilum lymph nodes are not shown on the X-ray film, unless they are of extraordinary size. Tuberculosis produces lymph nodes of this character. They are, however, rare in this vicinity, and, when seen, must be differentiated from similar changes occurring in other diseases.

The X-ray shadow of the normal hilum is largely the shadow of its blood-vessels and of the reflected pleura of which it is composed. The bronchi, being air-containing, yield but little shadow beyond the main bronchus, and, therefore, cannot be differentiated except, as not infrequently hap-

pens, a curving bronchus is caught end-on, and its shadow on the film is seen as a small ring, being the image of a cross-section of the bronchus involved, usually about 3 to 5 mm. in diameter

The so-called "thickened hilum shadow" may be due to the presence of undifferentiated, soft, lymph-node enlargement within the structure of the hilum, or engorgement or motion, or both, of its blood-vessels, from cardiac systole at the moment of exposure; or to films being made with slow-exposure technique (when the factor of motion is always present) and the normal variation in size and shape of these structures; for there is no fixed standard for the size and shape of the normal hilum and its shadow. Finally, the human element of the reader of the film must play a part in determining whether a given hilum shadow is within normal limits, or exceeds these. This personal factor, as everyone knows, is subject to variation from day to day, even in the same person.

Patients in these clinics reported as having "exaggerated hilum or lung markings" are dealt with by the clinical staff on the basis of this and other laboratory and clinical findings.

Shadows of axial vessels, that is to say, of vessels caught end-on, are small, dense, round or ovoid dots which, in single-film technique, may be (and many times have been) mistaken for calcified lymph nodes. They are readily differentiated by stereoscopic films, as are also many other shadows, whose value, in the single film, it is difficult or impossible to assess.

Childhood tuberculosis, when the lesions have begun to calcify, as they usually do eventually, is readily demonstrable by the X-ray film, and, unfortunately, we are obliged to wait for this in most but not all instances, before the diagnosis can be established roentgenologically. The calcium shadow is usually granular in character and is of sharply greater density than its surroundings. It has been shown by Opie (1) that the presence of calcium in the lesion does not necessarily imply that the lesion is healed. A soft, caseous lymph node may contain enough calcium to yield a definite shadow while it still remains an active, unhealed lesion. All calcification within the pulmonary structures is considered by the same authority (2) to be the result of tuberculous disease. The presence of these areas of calcification, therefore, whether they be within the lymph nodes or occur as isolated, minute areas within the lung parenchyma, where they represent a calcified primary lesion, is accepted as evidence of childhood-type tuberculosis. Unfortunately, they tell us but little as to the issue of activity or obsolescence. The great majority of the cases of child-

hood-type tuberculosis which we see are of this sort. Obviously, then, we are rarely able to complete the diagnosis in this disease until comparatively late in its progress. It may be said, however, that the bulk of these cases come to the clinic for the first time in this condition and are even then brought into the clinic as contacts of a known case of phthisis, never having had symptoms referable to the condition found. A certain number of children known to have been contacts, and who come for periodical examination and whose first films are negative, show the development of calcification on films at a later date. These are, perhaps, children who had the disease at the time of the first X-ray examination, but were passed as clear because of the absence of calcification at that time,—our methods were (and still are) too clumsy to demonstrate it.

Through the course of time we have watched, by successive X-ray films of the same child, pneumonic shadows going through gradual resolution, requiring from a year or two to four or five years, leaving in the pneumonic area progressively sharpening shadows of striated fibrosis; and finally resulting in a deposit of calcium within the adjacent hilum area, and perhaps similar granular calcification at the site of the original pneumonia, thus clearly establishing the diagnosis of childhood-type tuberculosis. These cases, for the purpose of our own office classification, we call "childhood type in the making." The clinical manifestations in these cases have been found by the clinical staff to have been, for the most part, ill-defined or absent, and commonly entirely escape detection or recognition. We now have such a considerable series of cases of this kind that they are no longer a rarity, and they lead me to guess that probably all of the many cases that we see with the classical or characteristic calcified tubercle somewhere (and it may be anywhere) within the lung parenchyma, accompanied by granular calcification within the hilum, and which constitute the greater number of the cases of the childhood type seen, represent the end-result of the above-described group "in the making," and did not come under observation during the transitional involuting stages.

These observations have led us to regard all fibrosing lung parenchymal areas in the child (which are obviously not those of adult-type phthisis) as probably belonging to the childhood-type group. They have taught us also to regard all pneumonic shadows in the child as potential tuberculous pneumonias, which may proved to be the very earliest manifestation in a given instance of childhood-type tuberculosis. Those pneumonic shadows that promptly disappear are, obviously, of the ordinary pneumo-

coccus type. On the other hand, when after the lapse of six months or a year they persist in whole or in part, we may confidently expect to see at a later date the development of the characteristic shadows of calcification, which afterward remain permanently for life. These old childhood-type lesions have been observed in such considerable numbers in adults as well as in the children in these clinics as to suggest that perhaps, after all, there may be a grain of truth in the old immunity theory.

The writer is impressed with the large number of children having childhood-type lesions who have been watched for a long period of years without developing the adult type of the disease. We are finding more children with the adult type alone than we are of those having the adult type superimposed upon the childhood type.

The writer is further impressed by the large number of adults (380, or $7\frac{1}{2}$ per cent) showing childhood-type lesions without adult phthisis, while 1,134, or $22\frac{1}{2}$ per cent, of the total, had manifest adult phthisis, in whom the characteristic lesions of the childhood type were not in evidence. Of the 92 adults having evidence of both childhood and adult types, it has been noticeable that the superimposed adult lesions were, frequently, moderate or minimal in extent and showing evidence of fibrosis and healing. In a small minority of this group (to prove the rule) the phthisis was extensive or advanced.

Did the large number, at all ages, showing childhood type alone, escape adult phthisis because of, or in spite of, their childhood lesions?

Did the large number with adult phthisis, not showing the usual demonstrable childhood-type lesions, develop their phthisis because of, or in spite of, the coincident absence of roentgenologically-demonstrable childhood-type lesions?

Does childhood infection with tuberculosis, of such character as not to kill and at the same time of such character as to leave permanent roentgen evidence of its presence, impart to the patient a measure of immunity which is an asset, in that it affords a protection against further ravages of the disease, or reduces a possible later phthisis to a modified and less virulent form?

These observations are offered as a contribution to the study of this problem.

REFERENCES

(1) Jour. Am. Med. Assoc., Oct. 18, 1930, p. 1153.
(2) Personal communication.

TUBERCULOSIS IN NEGRO CHILDREN[1]

COLE B. GIBSON[2]

At first thought, it might seem strange that the material for a discussion of tuberculosis in negro children should issue from a sanatorium in Connecticut. This state, as may be imagined, ranks well down the list in the matter of negro population,—38th to be exact.

Our interest in this subject will be understandable when the following facts are considered:

1: For the past seven years, in every 500 persons comprising the population of Connecticut there were 12 Negroes. During the same period, in every 500 admissions to this children's sanatorium, 41 were colored youngsters.
2: During the past seven years we have admitted 763 boys and 726 girls. Of these, 61 were negro boys and 64 were negro girls. During these seven years 71 deaths have occurred, and in this group were numbered 20 colored children. If we extend this further we find that in about every 25 white children admitted we have one death; whereas, among every 25 colored children admitted, four succumb.

This set of circumstances, it seems to us, bristles with interrogation points, and requires a very particular investigation. We recognize that the situation here reported probably exists elsewhere in many parts of the country on approximately the same scale, depending somewhat upon the density of the negro population. Almost everyone is familiar with the plentiful statistics which attest that the tuberculosis mortality rate is much higher in Negroes than in whites in the United States.

It is true that we have at hand stock answers for our interrogation points. These answers dwell lengthily, albeit somewhat vaguely, on racial immunity, and upon the dissimilarity between tuberculosis in Negroes and tuberculosis in whites as being due to a difference in inherent resistance, or to environmental peculiarities, or to unlikeness in lymphatic systems, skin pigmentation, and sizes of certain organs. For the present, at least, we must admit that lack of scientific proof prohibits

[1] Read at a meeting of the Connecticut State Tuberculosis Commission with the Staffs of Connecticut Sanatoria.

[2] Undercliff Sanatorium, Meriden, Connecticut.

the free acceptance of any of these answers as the full and complete explanation of the complex question of tuberculosis in the Negro.

In the meantime, it is clear that the entire problem is of vast importance and of such a nature that it should receive broad and searching attention, not only as a possible avenue toward the reduction of negro mortality but also for salient information as to tuberculogenesis that may be thus obtained.

In 1926 Carter (1) reported his observations made on negro patients in certain Virginia sanatoria over a period of ten years or more. Opie (2), in 1930, published a succinct contribution on the epidemiology of tuberculosis in Negroes. Brock and Black (3) studied tuberculosis in Negroes, giving particular attention to the haematological aspects. Pinner and Kasper (4) recently published a splendid article on tuberculosis in the American Negro, in which they reported their postmortem findings on 303 Negroes. Opie, McPhedran, Hetherington, *et al.* (5), in their survey of Philadelphia school-children, obtained valuable information from roentgen studies and tuberculin reactions in negro children; and with the latter procedure Aaronson (6) tested a large group of colored children in Tennessee. However, these two latter investigations were not concerned primarily with tuberculosis in Negroes in either instance, and information of this nature was brought to light incidentally in the course of certain broader studies.

Other important comments on the general subject appear in the literature of recent years, but we have been unable to find the report of a study devoted exclusively to tuberculosis in negro children. Working with such a small series of cases we naturally cannot expect to contribute very much toward the solution of this perplexing matter. We do believe, however, that our observations may prove of interest in so far as these relate to and emphasize certain peculiarities in the behavior of tuberculosis in the Negro and particularly in negro children.

First, let us analyze our 125 negro children by the examination of certain characteristics that appear in the grouping of these youngsters.

TABLE 1

Age-distribution

6 MONTHS TO 1 YEAR	13 MONTHS TO 2 YEARS	2-3	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	9	7	6	6	14	13	12	9	13	6	2	7	8	7	4	1
							Age at death									
		2		1	3	1	3	1	3				1	2	2	1

Age: The average age at time of admission of our negro patients was seven years and six months. The average age of white children admitted is almost nine years. Consultation of table 1 reveals that only 16 per cent of our colored patients were over twelve; whereas 24 per cent of our white children are beyond that age. Of our Negroes, 34 per cent were under six years of age, and 73 per cent were below ten. In other words, we were impressed with the fact that our colored patients, as a class, were definitely younger than our white children. What impressed us more, though, was the evidence that clinical disease of serious nature, as will be shown later, was more prevalent among the younger class of Negroes. This is further emphasized somewhat by the admission ages of those colored children who died, 70 per cent being below the age of ten years. The figures of Pinner and Kasper on this phase are interesting. In 303 autopsies on Negroes dead with tuberculosis, they found the age-group of below ten to be the largest, or 32 per cent of the total. In the same survey, 219 autopsies on white tuberculous patients contained but 7.3 per cent in the age-group below ten years, the smallest percentage of any age-group in the entire series.

TABLE 2

Tuberculosis contact

	TOTAL	POSITIVE TUBERCULIN	NEGATIVE TUBERCULIN	CLINICAL TUBERCULOSIS	NO CLINICAL TUBERCULOSIS	DEATH
History of contact.....	68	60	8	53	15	12
No history of contact.....	43	38	5	30	13	5
Questionable contact.....	14	10	4	8	6	3
	125	108	17	91	34	20

Contact: Opie (*Amer. Rev. Tuberc., 1930*) has remarked that "observations made postmortem suggest that the American Negro escapes tuberculous infection during childhood more frequently than white people." He offers as an explanation of this that "Adults of the white race suffer with long continued tuberculosis . . . . and during a long period they are able to be about and scatter widespread tubercle bacilli in relatively small numbers." Negroes "suffer with an acute type which causes profound illness and rapidly ensuing death" and they "scatter tubercle bacilli in vastly greater number for much shorter periods of time. . . . . They tend to transmit the same acutely fatal disease among those with whom they

are in intimate contact and apparently have little opportunity to disseminate minor infection widely." Our group of negro children, however, fails to provide proof that they escaped tuberculous infection while living in household contact with tuberculous patients. It will be seen from table 2 that 68 of our 125 patients gave a history of exposure to a person with tuberculosis. Of the contact group, 60 underwent tuberculous infection as proved by positive tuberculin reactions, and 53 presented evidence of clinical tuberculosis; 26 suffered with a serious form of the disease and 12 of these succumbed; 27 were found to have benign tuberculous disease; and the remaining 7 positive reactors revealed no signs of clinical tuberculosis. It is true that here we are dealing with a highly concentrated group, in that all of these children were suspected of or diagnosed as having tuberculosis prior to admission. Nevertheless, it is interesting to note that of these children who underwent known exposure to tuberculosis only 8 per cent escaped infection recognizable by antemortem examination. A further examination of our contact cases brings to light that several family groups of two or more children underwent household exposure to an adult with tuberculosis. In view of the generally accepted beliefs as to the danger of such contact during childhood the behavior of these children was noteworthy.

TABLE 3

Family groups of negro children

FAMILY	NUMBER OF CHILDREN IN FAMILY	NUMBER IN SANATORIUM	NUMBER OF KNOWN CONTACTS	NUMBER KNOWN TO BE INFECTED	MILD CLINICAL DISEASE	SERIOUS CLINICAL DISEASE	DEATHS
A N	4	2	+	3	0	2	1
A U	4	2	+	2	1	0	0
B E	7	2	+	3	1	2	2
B O	7	6	+	5	2	3	1
B R	2	2	+	2	0	0	0
H A	3	3	+	1	0	1	0
J A	2	2	+	2	1	0	0
K I	2	2	+	1	1	0	0
P O	3	3	+	3	3	0	0
Q U	4	3	+	4	2	2	2
R O	6	2	++	2	1	1	0
S H	3	2	+	3	1	1	1
S L	4	2	++	4	1	2	2
T A	11	4	++	11	4	2	1
W I	3	2	+	2	1	1	1
W L	4	3	+	4	2	2	2
	69	43		52	21	19	13

From table 3 it will be observed that in 16 families 69 children were in household contact with one or more patients with sputum-positive tuberculosis. Information as to infection in 17 of these children was not available but 52 were known to have been infected. Forty developed tuberculous disease; and this was of serious nature in nineteen, of whom thirteen died.

TABLE 4

Tuberculin reactions

	TOTAL	POSITIVE CONTACT	NEGATIVE CONTACT	QUESTIONABLE CONTACT	CLINICAL TUBERCULOSIS	NO CLINICAL TUBERCULOSIS	DEATH
Positive tuberculin.....	108	60	38	10	89	19	18
Negative tuberculin....	17	8	5	4	2	15	2
	125	68	43	14	91	34	20

Tuberculin: Using the intracutaneous method, 102 of these colored children reacted positively to a 1–1000 solution of Old Tuberculin at first test. Four reacted positively to the same dilution when the test was repeated after an initial negative response. Two reacted positively to a 1–500 solution after twice having failed to respond to the weaker dilution. In 19 of this group of 108 who had positive tuberculin reactions, signifying infection with tubercle bacilli, no clinical evidence of the disease or of the causative focus of infection could be found. Seventeen children failed to react to tuberculin. Five of these gave no history of contact with a tuberculous patient and presented no clinical evidence of tuberculous infection or disease. Eight gave a history of contact but evidenced no signs of tuberculous infection or disease. Two children who failed to react to tuberculin were found to have clinical evidence of tuberculous involvement. One of these was a six-year-old girl with far-advanced sputum-positive pulmonary tuberculosis; another was moribund on admission with tuberculous bronchopneumonia.

Clinical Manifestations: Commonly, white children with tuberculosis admitted to this sanatorium fall readily into one of several groups. Their disease, as a rule, is limited to one organ or to a single anatomical location, such as lung, bone, peritoneum, or lymphatic system. Complications or metastases to other organs or portions of the body do occur occasionally in children said to be suffering with "massive infection" or with the disease in its terminal stages. These occurrences are the exception

rather than the rule, however, and in general the disease in our white children behaves in conformity with the usual picture of tuberculosis in people with our present stage of immunity.

In tuberculous disease of the lungs, for instance, we are wont to recognize three characteristic manifestations. The freshly produced primary pulmonary tuberculosis, or epituberculosis, or perifocal tuberculosis is seen most often in very young children or infants. This is the lesion which is produced by first infection of the virgin lung soil with *Bacillus tuberculosis*. The lesion may be small and localized, or it may occupy an entire lobe. It is characteristic that the draining hilar lymph nodes are invariably involved in this form of the disease, constituting the primary complex of Ranke; but in white children these lymph nodes are seldom visualized in X-rays until calcification has followed caseation. Superimposed tuberculous infection upon such a nascent tuberculous lesion is responsible, we believe, for an occasional case of tuberculous bronchopneumonia or widespread caseous pulmonary tuberculosis, and in children so diseased death usually follows.

Recovery is the rule with the simple primary lesion. The parenchymal focus may undergo complete resorption or it may shrink to a calcified nodule of variable size, known as a Ghon's focus. The hilar lymph nodes draining the involved pulmonary area may undergo calcification with or without X-ray evidence of the parenchymal focus.

The National Tuberculosis Association classes these forms of the disease as "childhood tuberculosis." For ease in historical recording, and to give a more definite description, we feel that we might better refer to the freshly established, more or less acute, lymphatic-involving tuberculous pulmonary lesion resulting from first infection as *pulmonary tuberculosis, primary, manifest.* Since it is often several years before these primary lesions undergo resorption to the stage of calcific deposits in the hilar lymph nodes with or without a calcified parenchymal nodule, lesions in the process of undergoing such changes, unaccompanied by signs of tuberculous toxaemia, might better be called *pulmonary tuberculosis, primary, regressive.* In children who are obviously well and not interfered with by tuberculous toxaemia, well-calcified hilar nodes with or without calcified parenchymal nodules might better be described as *pulmonary tuberculosis, primary, obsolescent.* Thus, the terms *manifest, regressive,* and *obsolescent* will serve to indicate a different period in the chronology of the pathological manifestations that occur in virgin lung soil following first infection with tubercle bacilli. The residual evidence

of an antecedent primary lesion is by far the most frequent manifestation of tuberculous disease in the lungs of children.

Adult pulmonary tuberculosis is encountered in about 12 per cent of our white children. Having undergone primary infection with tubercle bacilli and thereby having consequently established an allergic state, a subsequent infection has produced a chronic tuberculous lesion tending to localize and fibrose with all of the usual characteristics of secondary pulmonary tuberculosis.

In our white children, bone tuberculosis is not frequently accompanied by pulmonary tuberculosis; and pulmonary tuberculosis, particularly secondary, usually conforms with the implications of the term *isolated phthisis*.

Tuberculosis in negro children presents some rather striking differences in behavior and in clinical manifestations.

The following list enumerates the diagnoses established in our group of 125 negro children based upon physical and laboratory examination and X-ray study.

No Clinical Tuberculosis

No disease	10
Nontuberculous	6
Tuberculous infection, no clinical disease	18
	34

Clinical Tuberculosis

Single Lesions

Pulmonary, primary, manifest	9
Pulmonary, primary, regressive	11
Pulmonary, primary, obsolescent	4
Pulmonary, secondary (adult)	8
Peritoneal	4
Lymphatic	1
Ocular	1
Tracheobronchial (negroid)	14
	52

Clinical Tuberculosis

Multiple Lesions

Pulmonary

Primary, and lymphatic	5
Primary, lymphatic and ocular	1
Primary and ocular	2
Primary and tracheobronchial	1

Primary, tracheobronchial and peritoneal	1
Primary, peritoneal and bone	1
Primary and peritoneal	1
Primary, bone, vertebral and lymphatic	1
Primary and vertebral	1
Secondary and lymphatic	1
Secondary lymphatic and ocular	1
Secondary and bone	1
Secondary and vertebral	1
Secondary and peritoneal	2
Secondary, peritoneal and lymphatic	1
Secondary, peritoneal, tracheobronchial and ocular	1
Tracheobronchial, bone and vertebral	1
Tracheobronchial, peritoneal and lymphatic	1
Tracheobronchial and lymphatic	3
Tracheobronchial, vertebral and peritoneal	1
Tracheobronchial and vertebral	1
Tracheobronchial and peritoneal	4
Extrapulmonary	
Vertebral and lymphatic	1
Peritoneal and lymphatic	2
Lymphatic and ocular	2
Lymphatic and skin	1
	39

It is of interest to note that in those 91 colored children, determined as having some form of clinical tuberculosis, but 12 were found whose disease was entirely extrapulmonary. Moreover, it seems noteworthy that but 52 of these children, by clinical investigation, presented tuberculous lesions confined to one organ or anatomical location; these are classified above as single lesions. Thirty-nine children were found to have evidence of tuberculous disease in two or more organs or anatomical locations, grouped above as multiple lesions.

Having in mind what was said previously about primary pulmonary tuberculosis and its invariable accompaniment of tracheobronchial involvement it may seem strange that in the above we have included a separate listing of tracheobronchial tuberculosis. Our purpose in this was to focus attention upon one of the most characteristic clinical signs of tuberculosis that we have observed in our negro children: massive enlargement of the tracheobronchial lymph nodes. McPhedran and others, from time to time, have discussed this somewhat curious and predominantly racial manifestation. McPhedran (7), particularly, has pointed

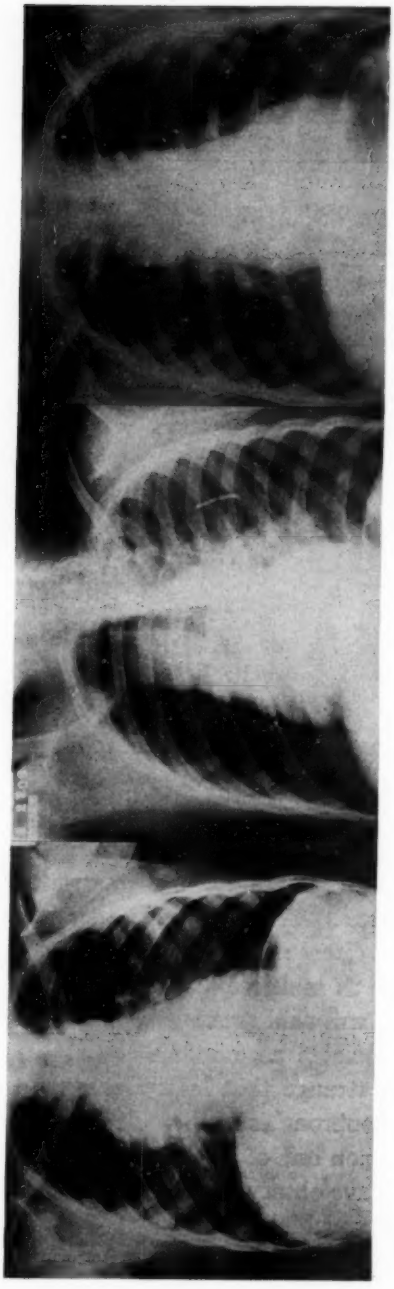

FIG. 3

FIG. 2

FIG. 1

out that "in colored children, both before and during school years, demonstrable uncalcified tracheobronchial nodes are not uncommon." He was able to follow 11 colored children past infancy who presented demonstrable lymph nodes in association with pulmonary infiltrations. He observed other colored children with demonstrable caseous nodes without pulmonary infiltrations. From his careful studies it is evident that uncalcified nodes situated beside the trachea and bronchi cast no shadow unless they are so far enlarged as to bulge out the mediastinum. While this occurs occasionally in white infants undergoing the effects of primary pulmonary tuberculosis it is comparatively rare. In our negro group it was quite common, having been observed in 28 children. (See figure 1.) Fourteen of this group presented no evidence of tuberculosis elsewhere, whereas an equal number were found to have multiple lesions.

This group is listed as follows:

Tracheobronchial without pulmonary infiltration or lesions elsewhere	14
Tracheobronchial associated with primary pulmonary infiltration	2
Tracheobronchial associated with peritoneal	4
Tracheobronchial associated with lymphatic	3
Tracheobronchial associated with peritoneal and lymphatic	1
Tracheobronchial associated with peritoneal and vertebral	1
Tracheobronchial associated with peritoneal, secondary, pulmonary, and ocular	1
Tracheobronchial associated with vertebral	1
Tracheobronchial associated with vertebral and bone	1

Pinner and Kasper in their report of autopsies called particular attention to the massive caseation of lymph nodes in negro adults, considering this to be practically diagnostic of tuberculosis in that race. They found, however, that in most cases "it was evident that these nodal lesions were not a part of the primary complex, because different groups of lymph nodes showed the same changes, because a calcified primary complex might be demonstrated in the same or another organic system, and because at times such lymph nodes were involved which on account of their topographical relations could not possibly have been the seat of a primary infection."

Even though in our cases we lack the postmortem proof that was theirs, yet our clinical observations of the types of multiple lesions sometimes associated with demonstrably enlarged tracheobronchial lymph nodes urges us to think that such patent evidence of lymphatic involvement in Negroes is not always necessarily part of the primary complex, although such is usually the case.

Close study of X-ray films revealed evidence of a parenchymal lung

focus of disease in 15 cases, whereas 13 presented only signs of bulging tracheobronchial lymph nodes. It is true that the causative parenchymal focus in these might have been completely resorbed prior to coming under our observation. Twenty-three of these children were below ten years of age and five were above that age. All had negative Wassermanns save one boy with a one-plus reaction.

The oval shadow bulging beyond the normal limits of the mediastinum or hilum is striking in posteroanterior films, although films taken in the oblique position will often reveal the enlargement even more clearly. (See figure 2.) The location of these nodal enlargements in our group were twelve on the right side, ten on the left side, and six bilateral. Most often, when the enlargement appeared on the left it was situated beside the aortic curve and was probably due to the lymph node above the left bronchus. Enlargements on the right side were most often at the level of the 2nd interspace, less often at the level of the hilum, and still less often at both locations. Bilateral enlargement was seen in 6 cases. One of these, a mulatto boy, also had enlarged cervical and axillary lymph nodes and was thought to have Hodgkin's Disease until biopsy of a cervical node proved the condition to be tuberculous. (See figure 3.) Another boy with enormous bilateral enlargement developed striking symptoms of pressure on the trachea. (See figure 4.) Following deep X-ray therapy, these nodes became reduced and finally, so far as could be determined by X-ray, returned to normal size. The boy is still under treatment, however, for tuberculosis of the spine. None other of these patients presented symptoms due to tracheal pressure.

Although it would seem that bilateral lymph-node enlargement should be regarded as exceedingly serious, it is interesting to find that only one or our 6 children of this type succumbed; this in spite of definite tuberculosis also present in other locations in the bodies of all.

In so far as we could determine by X-ray examination, the majority of these children attained complete reduction of their enlarged lymph nodes. In these, calcific deposits occurred in a few, but the greater number recovered without definite evidence of such pathological change.

Six of our patients with massive enlargement of tracheobronchial lymph nodes died, all having complications, or associated tuberculous disease, as follows:

Peritonitis	2	Peritonitis, secondary, pulmonary	1
Peritonitis and lymphatic	1	Bone and disseminated	1
Peritonitis and meningitis	1		

Aside from those patients with demonstrably enlarged tracheobronchial lymph nodes it will be observed by consultation of the foregoing list of clinical manifestations that 51 of our 125 patients revealed evidence of pulmonary tuberculosis. Twenty-seven of these children, with no demonstrable tuberculosis elsewhere, presented signs in their lungs considered by us to be due to primary tuberculosis. Four children of the average age of 12 years, 3 months, were classified as having pulmonary tuberculosis, primary, obsolescent, on the evidence of firm, calcified deposits in the hilum, with or without Ghon's foci, all being free from symptoms of tuberculous toxaemia. Eleven children of the average age

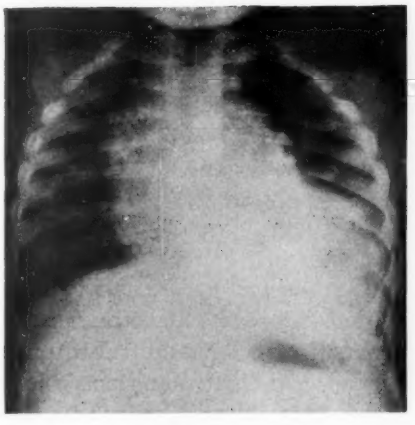

FIG. 4

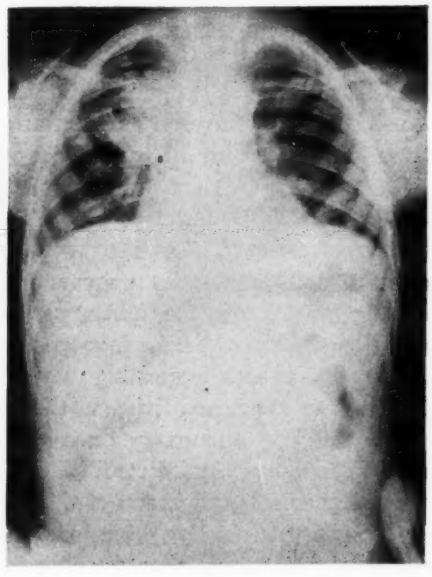

FIG. 5

of 8 years were found to have regressive primary lesions, as evidenced by increasing deposits of calcium in hilar lymph nodes with or without Ghon's foci. Nine children of the average age of 3 years presented evidence of parenchymal lesions of perifocal or epituberculous nature. Three of these evidently had suffered superimposed infection and succumbed to tuberculous bronchopneumonia. In several children having manifest primary lesions we were able to follow the gradual resorption and shrinking of the parenchymal infiltration until complete clearing of the lung field occurred with establishment of calcification in the draining hilar nodes.

One boy in this group was particularly interesting as were the other members of his family. He was the sixth of seven children. The father died with tuberculosis on May 30, 1928. The oldest boy, at the age of 15, was admitted to Cedarcrest Sanatorium in May, 1930, with pulmonary tuberculosis. During 1928 and 1929, all of the other children were in Undercliff. Jesse and Albert, the next two, were found to have typical "negroid" enlargement of the tracheobronchial nodes, and are included in that foregoing list. Clara, the fourth child, also suffered with that condition and tuberculous peritonitis, and died. Naomi and Lily Ruth, the fifth and seventh children, were found to be entirely negative for tuberculosis, even failing to respond to thrice-repeated tuberculin testing. James was admitted to Undercliff eleven months after his father's death, at the age of two years, with a parenchymal infiltration of the right upper, believed by us to be a primary lesion. (See figure 5.) Films in three months revealed some clearing of the infiltration, but an increase in febricity two months later was followed by increase in the extent of involvement. Four months later, after another period of increased febricity to as high as 105°, an infiltration was visualized in the left lower. Six months later, a similar incident occurred with involvement of the midportion of the left lung-field. In January, 1930, the boy developed measles and, after convalescence from this, his irregular fever ceased, and there followed gradual clearing of the previous pulmonary infiltrations. At present, the former enormous shadow in the right upper lobe has shrunk to a small dense shadow at the mesial end of the 1st interspace. No calcification is visible at this time. For us, it has been interesting to speculate as to possible explanations of the fact that in 7 children living in the same environment of exposure three developed serious pulmonary disease, two rather benign lesions, and two remained apparently uninfected. It is even more interesting to theorize as to the pathological explanation of the noncharacteristic behavior of tuberculosis in the two-year-old boy discussed. Bearing in mind that subsequent lesions appeared five months after his admission to the sanatorium and sixteen months after his father's death, we sense a possible explanation in the following statement of Pinner and Kasper: "Haematogenous propagation can and does occur very frequently without any break of a focus into the vascular bed. Very often, bacilli may reach the blood stream by way of the lymphatics. Ghon has shown convincingly that this process of lymphoglandular endogenous reinfection is often responsible for postprimary lesions."

It will be observed from the listed diagnoses that 14 other children presented signs of primary pulmonary tuberculosis and also had tuberculous disease in other organs of the body. Four of these children had manifest parenchymal infiltration and three of these we were able to observe over a considerable period while resorption of the epituberculosis proceeded.

The fourth died with peritonitis and widely disseminated tuberculosis. The primary lesions in the other ten were of regressive or obsolescent nature, and after observation were recognized to be of less importance than the lesions elsewhere. All of these children did well except one five-year-old boy who, although his primary lung focus appeared to be obsolescent, had, in addition, tuberculosis of the spine, multiple bone tuberculosis and suppurating lymph-node tuberculosis, and who developed meningitis and died.

In general, therefore, those children who had primary pulmonary tuberculosis, complicated or uncomplicated, made fairly satisfactory progress. This was true in the majority of those youngsters found to have parenchymal infiltrations of the primary order so long as superimposed infection, if it occurred, did not give rise to tuberculous bronchopneumonia. Those children with signs of primary pulmonary lesions in the process of regression always made satisfactory progress except in a few instances in which extrapulmonary or subsequent tuberculous disease developed.

Negro children with secondary or adult pulmonary tuberculosis of any greater extent than minimal almost invariably failed to recover. Four of our patients had minimal lesions of this type; one with lymphatic and ocular tuberculosis achieved satisfactory arrest. The fourth, suffering with bone tuberculosis in addition, remains under treatment. One girl, admitted with moderately advanced pulmonary tuberculosis, is approaching an advanced stage. Eleven children with advanced pulmonary tuberculosis, six uncomplicated, died of the disease. No negro child who ever had positive sputum recovered. The average age of these children with secondary or adult pulmonary tuberculosis was eleven years. The average length of illness of those patients who died was about eight months, according to histories which we were able to obtain. This is considerably shorter than the length of illness of our white children who died with adult pulmonary tuberculosis, which, as we observed (8) in a previous communication in 1927, averaged about one year and seven months in 87 patients. Since that time, this average has increased to slightly over two years. None of our colored children with this type of tuberculosis lived longer than two years after onset of the disease.

Again consulting our list of diagnoses we find 9 patients listed with tuberculosis of the bone. The most frequent site involved was the spine, being seen in seven of these cases. Two children not only had Pott's disease, but had bone tuberculosis elsewhere as well. An unusual fea-

ture of this group is that eight of the 9 cases of bone tuberculosis also had pulmonary tuberculosis of primary or secondary nature, or presented enlargement of the tracheobronchial lymph nodes.

These are circumstances not frequently met in our white children. On occasion, we have observed residuals of primary tuberculous infection in some of our white children who are afflicted with bone tuberculosis, but not often have we seen frank secondary or manifest primary pulmonary lesions in these youngsters.

Peritoneal tuberculosis was encountered frequently in our colored children. As will be seen from the list, it was found associated with lymphatic, pulmonary (both primary and secondary), and bone tuberculosis. In four of our 19 patients with peritonitis we were unable to discover any clinical evidence of the disease elsewhere. The adhesive and serous forms of the condition were about evenly divided, the prognosis being somewhat worse in the former. In only one of our patients who recovered from peritonitis could we later detect by X-ray any calcification of the mesenteric lymph nodes. This boy, a mulatto, also presented a calcified primary nodule in his lung, with accompanying calcific deposits in the hilum.

Nine of our 20 patients who died had peritoneal tuberculosis, in all instances associated with tuberculous involvement elsewhere.

Our 20 patients who died ranged in age from 2 to 16 years, the average being eight and a half years. The average length of illness of these patients, according to the histories we obtained, was one year and two months. Twelve of these children had tuberculous disease in more than one location. As already noted, pulmonary tuberculosis of secondary or adult type was the most frequent prime cause of death, and peritonitis was the most frequent complication.

A survey of this sort, tinctured as it must be with such a distinct statistical flavor, is not likely to give full and vivid expression of our somewhat complex opinions concerning tuberculosis in negro children. By a discussion of the behavior of tuberculosis in our group of negro children we have endeavored to point to certain manifestations as indicative of distinct differences as between white children with tuberculosis and colored children with the same disease. The difficulty in portraying these differences lies in the paradox that the differences do not always differ. For instance, certain white children under our observation have reacted to tuberculous infection and responded with tuberculous disease in a manner strikingly similar to that we have observed in Negroes.

Conversely, not a few of our negro children have behaved with their tuberculosis in exactly the same manner that is ordinarily expected in white children.

Actual clinical observation of these youngsters, study of their serial X-ray films, coupled with an attempt at grouping such as we have presented, has created some very distinct impressions, not to say opinions. The negro child by the violence of his reaction to primary tuberculous infection, by developing serious tuberculous disease at an earlier age, by the frequency of associated tuberculous lesions or complications, and by earlier surrender to lethal disease, depicts a characteristic picture that is more peculiar to the majority of colored children than to children of the considerably more immunized white race. In our own group, we have a hint of reiteration of this premise in the fact that our mulatto children usually progressed more favorably than the pure-blooded Negroes; and tuberculous disease in the mulattoes was more nearly in conformity with tuberculosis in white children than was that which was observed in their darker brethren.

The data which we have obtained from this clinical survey is not of a character that throws any direct light upon the reasons for the differences between the tuberculosis of Negroes and whites. If the variations that we have observed are due, as they undoubtedly are, to a lower resistance to tuberculosis in Negroes than in whites, we have obtained no certain evidence as to the cause of such lower resistance. However, we believe that our findings in relation to contact with tuberculosis, and our figures as to resulting infection and disease, and the bare enumeration of our clinical diagnoses strongly suggests that the opinion held by some, to the effect that lower resistance is due to a lack of childhood infection in Negroes, is not tenable.

One impression that we have is that the character of many lesions in our colored children suggested that these youngsters had met with a succession of tuberculous infections, and that to several such infections they had responded in the manner alleged to be characteristic of primary tuberculous involvement. In other words, we might conjecture that whereas first infection with tubercle bacilli in the white child modifies his resistance to future infections, similar immunological reactions do not occur in all colored children, even though they may develop a state of allergy in so far as positive response to tuberculin is concerned.

This would suggest, as Pinner and Kasper have already pointed out, the possibility of genotypic differences between the two races. Certain

genotypic variations might be responsible either for peculiar avenues of propagation of tuberculous disease, or might have an environmental effect upon the growth or virulence of infecting tubercle bacilli.

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CALCIFIED ABDOMINAL LYMPH NODES[1]

COLE B. GIBSON[2]

More and more, calcification of lymph nodes has come to be regarded as the typical manifestation of a certain phase of pathological tuberculous involvement. This is particularly true in calcification of the tracheobronchial and cervical lymph nodes. It is well recognized, of course, that the mesenteric lymph nodes may be subject to tuberculous disease. They are practically always involved in intestinal tuberculosis. More frequently, however, when the lymph nodes of the mesentery show evidence of tuberculosis there is apparent no associated disease of the intestine. Such limited disease is most frequently discovered and classified as a result of calcific deposits in the lymph nodes. Typhoid fever and parasitic infection have been suggested as causes of calcified mesenteric lymph nodes, but little evidence has been offered in substantiation. It seems generally agreed to regard such a process in the abdominal lymph nodes in the same manner as calcification of other lymph nodes.

The occurrence of calcified abdominal lymph nodes varies decidedly in different localities. Dunham and Smythe (1) found evidence of calcified abdominal nodes in 21 of 120 children examined in New Haven, Connecticut. Opie (2), in 93 necropsies on children and 50 on adults, in St. Louis, found not a single case. Sternberg (3) states that mesenteric lymph-node tuberculosis is a quite common autopsy finding in Berlin. However, Beitzke (4) found but 10 instances in 1,100 specially examined necropsy cases at the Berlin Pathological Institute. Woodhead (5), in Edinburgh, found tuberculosis of the mesenteric lymph nodes in 78 per cent of children, and in 11 per cent it was the only lesion present.

According to Klein (6), the literature prior to the war had little reference to the condition; but in his opinion there seems little doubt that it has increased in both Poland and Germany since then. Certainly in the past seven or eight years increasing allusions to it have appeared in print.

According to the literature, most observers have become interested in

[1] Read at a meeting of the Connecticut State Tuberculosis Commission with the Staffs of Connecticut Sanatoria.

[2] Undercliff Sanatorium, Meriden, Connecticut.

the condition as the result of encounters with certain clinical manifestations, sometimes referred to as the "Sternberg Syndrome." This is understandable because the acute symptoms of the condition occasionally are quite suggestive of an acute surgical abdomen, such as might be caused by appendicitis, gall-bladder disease, intussusception, urinary-tract stone, gastric ulcer, or other similar accidents. Two of Dunham's patients were first seen in the hospital where they had been sent for appendicectomy. The clinical picture in each failed to measure up to the probable diagnosis, and abdominal roentgenograms revealed striking evidence of calcified nodes that were held to be the causes of the patient's acute distress.

Klein, who has seen 60 cases during the period when acute symptoms were manifest, describes the condition as follows: "The chief subjective symptoms are abdominal pain and vomiting from which the patient gets no effective relief. The pain may or may not be intense. It is sometimes dull, but more often it is sharp and colicky. It appears or is aggravated by pressure, and is often less severe after eating. It is apt to come in attacks which may be extremely severe and be accompanied by nausea and vomiting." Other clinicians report that the attacks often follow fatigue, strain, or other debilitating occurrences. Fever is said by some authors to be infrequent, while others report it as a common event during attacks or longer. The leucocyte count is not raised, nor does the remainder of the blood picture show anything of significance.

The characteristic feature seems to be the relation of pain to a swollen lymph node. Golden and Reeves (7) were rarely able to palpate such a mass, but found most often localized tenderness in the right lower quadrant, sometimes discovering two or three tender points. When felt, the tumor is generally hard and the size of a cherry. In Fertik's (8) series, this pain on palpation was found in the right hypochondrium in 46 per cent of the cases, and in combined right and left hypochondriac regions in an exactly similar number. Most often, observers have found the involved nodes situated usually in the lower part of the mesentery of the small intestine or medial to the caecum and ascending colon. Bagg (10) reports that in 15 of 30 cases they were located in the ileocaecal angle. Golden and Reeves found the calcified nodes usually below the third lumbar and above the second sacral segment, on either side of the midline, but more often to the right than to the left. In 23 of 29 of their cases they were in the right lower quadrant of the abdomen. These authors believe that "in earlier years the diagnosis was apparently never made

before operation or necropsy," and many observers agree that operation is often performed for abdominal tumor, appendicitis, intestinal obstruction, or because the violence of the symptoms seem to indicate surgical interference, only to find that calcified lymph nodes are responsible.

Some are of the opinion that the tuberculin reaction is of twofold importance in diagnosis. That is to say, a positive reaction indicates the certain existence of infection with tuberculosis, and also sometimes causes a painful swelling of the involved nodes. However, it must be clear that the diagnosis is doubtful unless there is a definitely palpable mass, or unless calcific infiltration of the nodes can be demonstrated by a roentgenogram of the abdomen.

Occasionally, as at the Presbyterian Hospital (New York), the surgeons will be impelled to operate knowing that lymph-node involvement is present, for fear that acute appendicitis may coexist. At times, other situations arise such as that described by Valentin (9) in 1921. He reported a case of occlusion of the ureter, with hydronephrosis, signalized by colicky pains and caused by tuberculous lymph nodes impinging on the ureter. Removal of the nodes resulted in permanent cure.

The acute symptoms described will undoubtedly direct attention to and set in motion the proper diagnostic machinery in many of these cases. It is likely, however, that a far greater number, whose symptoms are slight or obscure or absent, will not be discovered. Not so long ago it was a matter of some surprise to many clinicians to learn of the frequency of calcified tracheobronchial lymph nodes. They have come to appreciate now that such findings are indices of first infection with tubercle bacilli and that such an incident may pass unremarked and unsignalized during the childhood years. So it must be also with calcification of the abdominal lymph nodes. Whereas, the tracheobronchial lymph nodes receive their infection by draining an infection of the pulmonary parenchyma, which produces no striking symptoms, so similarly the abdominal lymph nodes may become harborers of tuberculous changes as a result of draining the intestine which has received swallowed bacilli.

It is well known that primary tuberculous infection of the pulmonic parenchyma may be in an area so small, and may undergo such complete resorption as to leave behind no identifiable residuum in the lung proper. Frequently, Ghon's foci are undiscoverable while striking evidence of calcific infiltration of the tracheobronchial lymph nodes is present. It is not inconceivable that somewhat the same procedure may occur in instances when tubercle bacilli are swallowed. The original lesion of

infection in the intestine may heal and leave behind nought but the evidence that its detritus was drained into the lymph nodes, and there, in the course of the tuberculous pathological processes, calcification was established.

Such a view is not in accord with the theories of many investigators who feel that the ingested tubercle bacilli pass through the intact intestinal wall to set up original infection in the draining nodes.

Whichever may be the correct assumption it still seems clear that abdominal lymph nodes may suffer tuberculous infection, and may undergo caseation and calcification; and these occurrences may be responsible for very striking symptoms or, on the other hand, may evidence no sign or at best may give rise to vague and indefinite manifestations. The latter group undoubtedly outnumbers the former and probably has a part of no little importance in our schemes of diagnosis and treatment of tuberculous children.

With this thought in mind we have investigated a group of children admitted to Undercliff with diagnoses of various forms of tuberculosis. The group comprises 200 current admissions and in only six was there any particular lead toward tuberculous involvement in the abdomen. All children admitted here are routinely tested with tuberculin and the great majority react positively. In these cases, even though clinical signs and symptoms are often obscure or absent, we have long sought to correlate this evidence of tuberculous infection with some site or lesion which might appear to be the probable responsible focus. In most instances we have been successful, but always a certain few remain unclassified.

Not infrequent and always trying problems are those children who are continuously below par in strength, growth, and behavior, and who have positive tuberculin reactions, with or without history of exposure to tuberculosis. Assiduous search often fails to reveal any other illness as a possible cause for the under normal condition, and pulmonary tuberculosis can be absolved as the causative agent by repeated roentgenograms and prolonged observation. Occasionally, these children may have lightly considered episodes of abdominal discomfort or at times that mooted vagary, "chronic appendicitis," may intrude as a transitory suspicion. In the majority, though, such signposts are absent or go unheeded, and the children are carried along as suspicious with no adequate explanation as to the underlying cause of their retarded physical progression. As a result of our recent investigations we are convinced that

roentgenograms of the abdomens of such children, in certain instances, will give entirely satisfactory answers to our questions.

An analysis of 200 current admissions gives the following information:

Repeatedly negative tuberculin reactions	22
Positive tuberculin reactions	178

Diagnoses by roentgenograms of chest and bones in the 178 positive reactors are as follows:

Probable and *positive tuberculosis:*		90
Tuberculosis, pulmonary, infantile	10	
Tuberculosis, pulmonary, juvenile (calcified tracheobronchial)	28	
Tuberculosis, pulmonary, juvenile (Ghon's focus and calcified tracheobronchials)	13	41
Tuberculosis, pulmonary, adult		23
Tuberculosis, bone		12
Tuberculosis, bone and pulmonary		3
Tuberculosis, miliary		1
		90
Suspected and *possible tuberculosis:*		
Tuberculosis, pulmonary, juvenile (calcified tracheobronchial) suspect		12
Nontuberculous pulmonary disease		13
Negative for tuberculosis of lungs or bone		63

Thus, by means of roentgenograms of the lungs and bones of these 178 positive reactors we discovered positive evidence of tuberculosis in 90 patients. Twelve patients were suspected of tuberculosis but the positive evidence was lacking. Thirteen were found to have pulmonary disease of nontuberculous causation. In 63 no evidence of pulmonary or bone tuberculosis could be demonstrated by X-ray but these were classified by clinical examination as follows:

Tuberculosis, lymph nodes (cervical, axillary, inguinal)	16
Tuberculosis, peritoneal	2
Tuberculosis, ocular	2
Tuberculosis, ocular, and peritoneal	1
Tuberculosis, ocular and glandular	1
Tuberculosis, skin and lymph node	1
	23
Tuberculosis, lymph nodes (cervical, axillary, inguinal) suspect	4
Tuberculosis, suspected, site undetermined	13
Nontuberculous disease	23

If, then, in our search for the reasons for 178 positive tuberculin reactions, we combine clinical evidence with X-rays of lungs and bones we arrive at this recapitulation:

Positive tuberculosis of lungs, bones, lymph nodes, skin, peritoneum, eye, and mixed forms		113
Suspected tuberculosis, juvenile type	12	
Suspected tuberculosis, site undetermined	13	
Suspected tuberculosis, lymph node	4	
	29	29
Nontuberculous pulmonary disease		13
Nontuberculous nonpulmonary disease		23
		178

From these figures it will be seen that we have explanations for all but 65 of our positive reactors. Thirty-six of these have definite nontuberculous diseases which in most instances are responsible for the symptoms and signs that caused their admission here. At any rate, these diseases are of so much importance that hidden foci of probably obsolete tuberculous infection are of no particular concern. But we are concerned with the suspect group of 29; here we have some reason for tentatively regarding these children as tuberculous although positive evidence is still lacking. It is interesting to observe the value of abdominal roentgenograms in this remainder. As a routine measure, roentgenograms of the abdomens of our 200 children were made. Using a Bucky diaphragm, films were first taken in the anteroposterior position at a distance of 30 inches. They were also made in the lateral position on all patients who in the anteroposterior position disclosed positive or suspicious evidence of abdominal calcification.

Nineteen patients were found to have abdominal calcifications, and all of these had positive tuberculin reactions. According to the previous classifications these patients were distributed as follows:

Suspected tuberculosis, site undetermined	9
Suspected tuberculosis, lymph node	3
Suspected tuberculosis, juvenile type	2
Bone tuberculosis	3
Tuberculosis, pulmonary, juvenile	1
Tuberculosis, peritoneal	1
	19

The location of these calcifications were as follows: Right side, 7; left side, 9; both sides, 2; and midline 1. Those on the right side most often

were near the level of the 5th lumbar vertebra, while those on the left were more frequently found near the level of the third lumbar.

On abdominal examination, one or more masses were palpable in four patients. Pain could be produced in one of these. No pain, no masses, and no tenderness could be found in the remaining 15 cases.

The following case-histories will serve to point out somewhat more definitely the great value of routine abdominal roentgenograms in children.

GROUP 1: SUSPECTED TUBERCULOSIS, SITE UNDETERMINED

R. H.: Admitted at age of 10. Had all diseases of childhood, and at age 7 developed cervical lymphadenitis which was operated upon. Has had repeated attacks of congestion of lungs since pneumonia at age of $3\frac{1}{2}$ years. These attacks are characterized by sharp pain in left axilla and in precordium, and last for a short time only. No history of attendant cough, expectoration or febricity. Under observation at New Haven Dispensary and has not been to school for past two months. On admission was 7 per cent overweight. Had a few lymph nodes, size of marbles, at angles of jaws. Intracutaneous test positive. X-ray of chest negative. Tentatively, patient was classified as having obsolete tuberculosis of the cervical lymph nodes. Abdominal roentgenograms revealed two calcified areas just above level of iliac crest on right side.

L. V.: Admitted at age of 10. Mother died of pulmonary tuberculosis at Shelton Sanatorium. One brother is patient at Undercliff with tuberculous hip. Prior to admission, had been losing weight and strength, and had afternoon temperature of 100°. Was standard weight on admission. Intracutaneous test positive. *Impression:* Nontuberculous, although this not definite in view of vague symptoms and history. Roentgenograms show undoubted calcification of abdominal lymph nodes and this fact, taken in connection with the bone tuberculosis of his brother and the pulmonary tuberculosis of his mother, causes the suspicion that infection in both boys may have been food-borne as a result of handling by mother. (See figure 1.)

B. H.: Admitted at age of 9. Mother and brother died of pulmonary tuberculosis. Has had cough intermittently for past year and a half. Sent to Undercliff with diagnosis of pulmonary tuberculosis verified by X-ray. On admission, was 6 per cent underweight and somewhat undernormal in appearance, but had no complaints. Intracutaneous test positive. Roentgenograms of chest negative. Tentative diagnosis of chronic hypertrophic tonsillitis was made. Abdominal roentgenograms revealed undoubted calcification at level

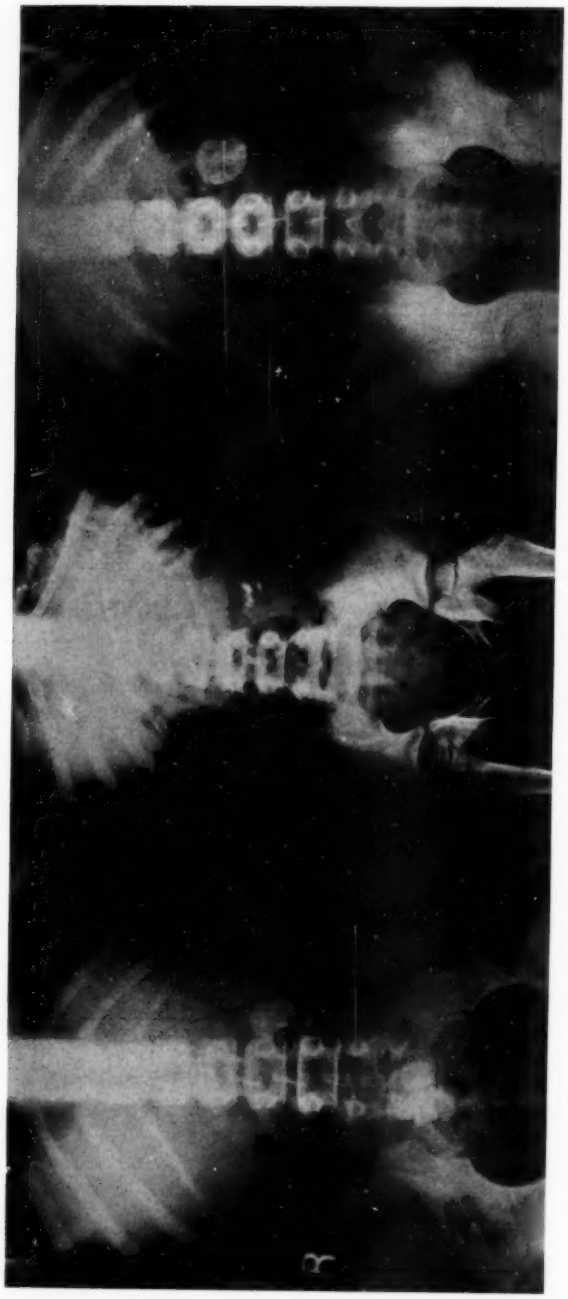

FIG. 1. CASE *L. V.*, GROUP 1

FIG. 2. CASE *B. H.*, GROUP 1

FIG. 3. CASE *E. S.*, GROUP 2

of 3rd lumbar vertebra. It is not unlikely that complete calcification is yet to be established and that, in the meantime, patient may evidence some effects of toxic absorption from the still active process. (See figure 2.)

M. A.: Admitted at age 12, with no history of exposure to tuberculosis. Had been under observation at New Haven Dispensary for some time, where the girl was suspected of having tuberculosis. On admission, was 27 pounds underweight, was pallid, and was obviously below par in strength and behavior. Intracutaneous test positive. X-rays of chest were negative, and clinically no evidence of other disease could be found. Abdominal roentgenograms revealed calcified masses at the 5th lumbar vertebra and level of 2nd sacral segment.

D. F.: Admitted at age 7. Mother died of peritonitis four years previously. For one year prior to admission, patient had lost strength, and had afternoon elevation of temperature and pains in abdomen. She was undernourished, pale, and 9 per cent below standard weight. Intracutaneous test positive. X-ray of chest negative and clinical examination revealed no other probable cause of debility. Roentgenograms of abdomen disclosed calcified lymph node at level of 3rd lumbar vertebra on left side. A smaller node was visible laterally to first node at level of 1st lumbar.

E. C.: Admitted at age 11. Mother died of tuberculosis five years previously. Father has tuberculosis. For well over a year patient had lost weight and had undue fatigue. She was 10 lbs. below standard weight on admission. Intracutaneous test positive. Had pyuria, which we were inclined to suspect as proximate cause of subnormal condition; but abdominal films revealed calcified lymph nodes in the right lower quadrant, somewhat confusing the picture. No urological condition could be determined in the New Haven Hospital. Shortly afterward, pyuria cleared, and we were left with very strong evidence that tuberculosis of abdominal lymph nodes was probably responsible for clinical picture.

H. I.: Admitted at age 11. One sister died of meningitis eighteen years previously. One uncle died of tuberculosis. Mother has questionable asthma. Patient was taken to New Haven Dispensary two years before, because she was not gaining and was running afternoon elevation of temperature. Had had no abdominal symptoms but X-rays taken there revealed calcified abdominal lymph nodes. Roentgenograms of chest negative. Anteroposterior and lateral plates of abdomen showed calcified abdominal lymph node at level of promontory of sacrum, almost in midline.

R. R.: Admitted at age 2. Mother and father both under observation for tuberculosis. Was underweight and pallid; otherwise, no clinical or X-ray findings. Intracutaneous test positive. She was discharged six months later and classified as having no disease. Admitted again five months later, with history of having had recurrent attacks of fever lasting three or four days about every two months for the past three years. X-ray of chest negative and no cause of febricity could be discovered. Roentgenograms of abdomen showed calcified lymph nodes on both sides of spine.

GROUP 2: SUSPECTED TUBERCULOSIS, CERVICAL LYMPH NODES

M. B: Admitted at age of 15 months. Mother died of tuberculosis. No X-ray evidence of pulmonary disease on admission. Small palpable cervical lymph nodes the only clinical finding. After five months patient was discharged, but was readmitted three years later. Was normal in weight but general appearance not sturdy. Both ears were discharging, and there was papular eczema of face, scalp, and thighs. Cervical lymph nodes definitely enlarged. Intracutaneous test positive. Patient gained weight slowly and intermittently. *Impression:* While the child was classified as having tuberculosis of cervical lymph nodes, it seemed unreasonable to assume that the condition was solely responsible for his subnormal condition. On two occasions, vague and indefinite abdominal discomfort caused his transfer to the Infirmary. We could assign no cause for either attack on account of the brevity of both and the absence of significant symptoms. Roentgenograms of abdomen not only supplied a probable explanation of these attacks but also suggested why this youngster had been so slow in improving his general condition, for several calcified nodes were visualized at level of 12th dorsal spine on right.

E. S.: Admitted at age 2. Previously, she had been treated at New Haven Dispensary for phlyctenular keratitis, malnutrition, and lymphatic tuberculosis. She left the sanatorium and was returned after two years, and has been in residence here since. She has always been a slight, small child; has gained weight very slowly, and at times it has been stationary for several months. She became fatigued easily but was rarely definitely ill. There were slightly palpable lymph nodes in the cervical region. Otherwise, physical examination and X-ray examination were not noteworthy. Intracutaneous test positive. Poor and capricious appetite, but no attacks of abdominal discomfort. At this time general condition is improved; gaining in weight more steadily, and sturdier in appearance. *Impression:* Tuberculosis, site undetermined. Roentgenogram of abdomen reveals large calcified node at level of 1st lumbar vertebra. It is interesting to contemplate the possibility that the beginning of improvement was coincidental with cessation of caseation and the definite establishment of calcification in the healed node. (See figure 3.)

E. B.: Admitted at age 8. No known history of exposure to tuberculosis. She had been undernourished for several years and had been in Wallum Lake Sanatorium (Rhode Island) for eleven months one year previously. General appearance poor; 18 per cent below standard weight; intracutaneous test positive. X-rays of chest were negative but, in spite of this, a juvenile pulmonary lesion was suspected, but this opinion was soon discarded; and while we continued to suspect her of tuberculosis the site could not be demonstrated. After gaining 9 lbs. patient remained stationary for 3 months and was then removed against advice, having been here for 11 months. Readmitted fourteen months later, still 12 lbs. underweight, after having been studied at several places. Gained 6 lbs. and then remained stationary again. General appearance somewhat improved, but we still felt that we were warranted in our suspicion of tuberculosis. Abdominal roentgenograms confirmed our suspicions, revealing calcified nodes at level of 2nd lumbar vertebra on right.

GROUP 3: SUSPECTED TUBERCULOSIS, JUVENILE

L. D.: Admitted at age 7. Mother died of tuberculosis four years previously. She had failed to gain weight and complained of undue fatigue, and on admission was slightly underweight. Intracutaneous test positive. Roentgenograms of chest not conclusive. Some question of calcified area showing through the cardiac shadow at level of 8th rib. For this reason patient tentatively classified as suspicious for juvenile tuberculous lesion. Abdominal roentgenograms, however, revealed significant evidence of calcified mesenteric nodes, probably the underlying cause of her lack of progress at home. (See figure 4.)

J. M.: Admitted at age 14. Well until six months before admission, when he was seized with generalized abdominal pain and vomiting. Sent to hospital, with diagnosis of acute appendicitis, where he remained for six weeks, but no operation performed. One month later had attack of pain on left side with some associated cough and elevation of temperature. On admission here, was 13 per cent underweight and intracutaneous test positive. X-rays of chest showed no definite tuberculosis. Number of nodules in both hila, but these were fibrotic in appearance though several in the right hilum were suspicious for calcific infiltration. Based upon these findings, a temporary classification of latent juvenile pulmonary tuberculosis was adopted. Roentgenograms of abdomen reveal undoubted calcified lymph nodes, probably the site responsible for much of his difficulty. (See figure 5.)

GROUP 4: POSITIVE TUBERCULOSIS ELSEWHERE

Peritoneal

C. O.: Negro boy, admitted at age 8. Mother died of tuberculosis since his admission. He was ill six months prior to entrance with fever, cough, loss of

weight and appetite, and abdominal pains. Intracutaneous test positive on admission. X-rays of chest suggested enlargement of tracheobronchial lymph nodes but his important difficulty was an exudative tuberculous peritonitis. Was constant bed-patient for more than a year. During first six weeks, he was moderately ill, but afterward he improved steadily until attack of pleurisy eighteen months after admission. Made uneventful recovery from this, and then continued steady progress which was only interrupted by a moderate attack of influenza, eight months later, which developed while patient was home on leave. Since that time he has gained consistently and is now without symptoms, and abdominal roentgenograms reveal calcification in lymph nodes.

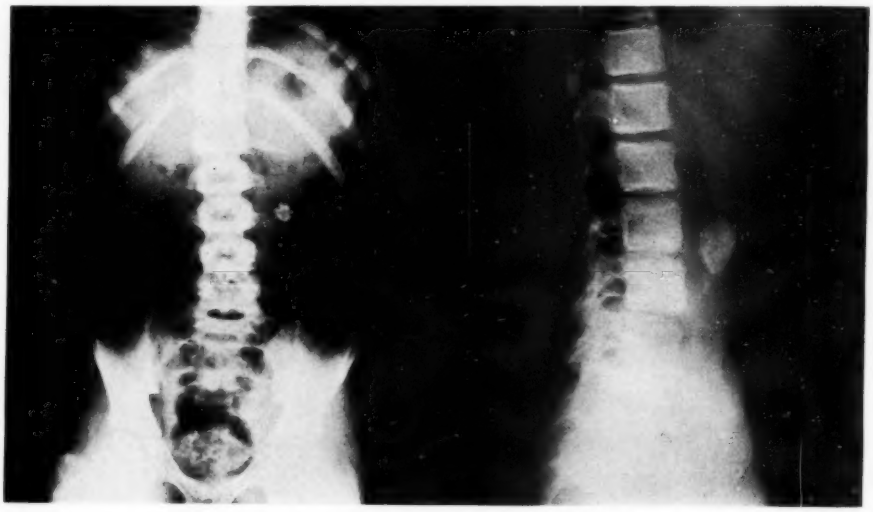

FIG. 4. CASE *L. D.*, GROUP 3

FIG. 5. CASE *J. M.*, GROUP 3

Pulmonary, juvenile

J. C.: Admitted at age 13. Father died of haemorrhage. Patient had pneumonia in 1919. For five years previous to admission had been subject to asthmatic attacks, worse in summer but continuing through winter at monthly or two-week intervals. Chief symptoms dyspnoea and cough. No history of sensitization to pollens or foods. Was 22 per cent underweight on admission. Intracutaneous test positive. Pallid and obviously poorly nourished. X-ray of chest revealed, on right side at posterior level of 8th interspace, a well-marked elongated oval arch of parenchymal calcification. Hilar region on right evidenced a number of calcified areas. This lesion was classified as obsolete juvenile pulmonary tuberculosis. He had several attacks of dyspnoea after admission. These were effectively relieved by ephedrine. Has had no

attacks in several months. Gave moderate reaction to dog hair, but was negative to everything else. Two months after admission, had attack of acute catarrhal jaundice from which he recovered in about ten days. There has been no recurrence. Thinking that the Ghon's focus in the lung was probably the site of his primary infection with tubercle bacilli, we are somewhat surprise to find clear-cut evidence of calcific infiltration in the abdominal lymph nodes.

Bone

S. H.: Admitted with tuberculosis of right hip. Routine films presented evidence of calcific deposits in abdominal lymph nodes.
C. T.: Admitted with tuberculosis of left hip. Routine films revealed presence of calcified abdominal lymph nodes.
G. C.: Admitted with tuberculosis of left hip and right tarsus. Routine films revealed signs of calcific deposits in abdominal lymph node and illustrate progressive development of this condition.

COMMENT

In our group of 200 children abdominal roentgenograms have brought to light 19 patients with calcified abdominal lymph nodes. For varying periods and for various reasons all of these children have been under definite suspicion for tuberculosis. In five, undoubted tuberculous disease had been demonstrated, three having bone tuberculosis, one peritoneal tuberculosis, and one pulmonary tuberculosis of the juvenile type.

The remaining 14 patients were not clear-cut. History of interrupted physical progress, indefinite symptomatology, positive tuberculin reactions, and lack of proof of any other existing disease were responsible for our attitude that each probably had tuberculosis or was undergoing the effects of first infection with tubercle bacilli. This seemed a safe view to take, even though the focus of the alleged or suspected tuberculous infection had not been demonstrated. The evidence revealed by abdominal roentgenograms serves to validate our suspicions in these cases and also points a significant finger toward others. We can but speculate as to the number we have missed, and we are convinced that the routine use of abdominal roentgenograms in children is a procedure of vast importance, not only for aid in diagnosis but also for the information and clues in tuberculogenesis that may come to light.

It is to be borne in mind, however, that a single plate may not give the desired intelligence. Serial roentgenograms of the abdomens of suspected children should be taken over a period of years. Tubercle-formation

and caseation in lymph nodes may proceed for a long time, and although strong suspicion may exist the diagnosis must be deferred until calcification begins and is demonstrable by X-ray. Often a year or longer is needed for this development. Moreover, it is well known that the establishment of calcification in one node does not warrant any termination of observation, since the node in question may still contain caseating portions, and other adjacent nodes may be caseating and liquefying, thus qualifying as sites of progressive tuberculous infection, and therefore as potentially dangerous.

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TUBERCLE BACILLI IN THE GASTRIC CONTENTS OF TUBERCULOUS CHILDREN

A Study of 59 Cases[1]

INA GOURLEY

A study of 59 children[2] in the Children's Building of Arroyo Sanatorium and Del Valle Preventorium has been made in the past two and a half years. Gastric lavage and guinea-pig inoculation have been done to determine the presence of tubercle bacilli. Gastric lavage has been used because children as a rule swallow their sputum instead of expectorating it.

Our interest in gastric lavage in children with pulmonary tuberculosis has been to determine if there is a group of children with parenchymal lesions free from tubercle bacilli. McPhedran's (1) classification of childhood lesions has one group designated as "C" which is supposed to have negative sputum. He, however, makes no mention of gastric contents. Our second interest in this study is to determine when the child who has been an open case becomes a closed one. In other words, when can the child, who has had an open lesion, be safely transferred from the sanatorium to the preventorium, or to a group of normal children such as in a public school.

REVIEW OF THE LITERATURE

Meunier (2) in 1898 first recommended gastric lavage and the study of the stomach contents for tubercle bacilli. In 1927 Armand-Delille (3) reported a study of 110 tuberculous children by gastric lavage. He found 31 per cent of these positive for tubercle bacilli. He, however, homogenized the gastric contents before staining for tubercle bacilli. In 1929, Poulsen, *et al.* (4), of Copenhagen, reported 15 cases with eleven positive and four negative. Zambrano (5) in 1931 reported 50 cases with only eight positives. Wallgren (6) of Gateborg, Sweden, reported gastric lavage on 40 children with erythema nodosum, with seventeen positive on guinea-pig inoculation. Kereszturi, *et al.* (7) reported in 1932 a study of 40 children. Gastric contents inoculated into guinea pigs gave positive results in 17.5 per cent of the children studied.

[1] From the Arroyo Sanatorium, Livermore, California.

[2] Dr. Ann Martin mentioned eleven of these cases in her article, *Tuberculous Pulmonary Infiltrations in Childhood, Amer. Jour. Dis. Child.*, October, 1932, xliv, 754.

J. Ligner of Gotenburg (8) was able to demonstrate tubercle bacilli in the gastric contents on one child in the preallergic period of tuberculosis. In 1931, Poulsen (9) reported 110 cases with 53 positive and 67 negative for tuberculosis. Poulsen examined the stomach contents by direct smear, plantings on Petroff's medium and inoculating guinea pigs. Poulsen not only examined the gastric contents of children with definite pulmonary lesions, but also ailing children with positive tuberculin reactions. In these he found some with positive stomach contents. He discusses at length whether or not so elaborate and expensive a procedure is warranted. He says, "It would seem natural and defensible to omit the test in all obvious cases of pulmonary tuberculosis." He at least implies that if there is a demonstrable X-ray lesion in the parenchyma in childhood tuberculosis the gastric contents would be positive.

Drucker (10) of Copenhagen has used gastric lavage in the study of children vaccinated with BCG. Thirty-five were found negative. One was found to have BCG organisms in the gastric contents six weeks after vaccination. A roentgenogram of the chest showed increased width of the mediastinum.

Clausen (11) of Copenhagen studied 53 children with pulmonary tuberculosis. The gastric contents were positive for tubercle bacilli in 55 per cent of the cases. It is of interest to note that 41 per cent of those with positive gastric contents were over 6 years of age, that is, of school-age.

Opitz (12) of Berlin has written a series of articles which appeared from December, 1928, to June, 1931. The gastric contents of 33 out of 36 children with epituberculosis were found positive on guinea-pig inoculation. Opitz's study also included children with enlarged hila, pleurisy, cervical adenitis, and bone-and-joint tuberculosis, and children with positive tuberculin tests but without demonstrable lesions. There were some children in each group with stomach contents positive for tubercle bacilli.

Friedländer (13) has studied the gastric contents of 12 children with tuberculous meningitis. He found tubercle bacilli by guinea-pig inoculation in five of the 12 cases.

Armand-Delille (3), Poulsen (4), Opitz (12) and Ligner (8) consider these children with positive gastric contents capable of infecting contacts. Opitz (12) is of the opinion that such children should be protected from reinfection by open adult cases and, in turn, that healthy children should be protected from these children who are harboring tubercle bacilli.

METHOD USED IN OUR STUDY

Gastric lavage has been done in the morning after the child has fasted at least six hours. Fifty to 200 cc. of sterile normal saline solution was used. Guinea pigs were inoculated and autopsied in from four to eight weeks. No animal was considered positive unless tubercle bacilli were

found. Poulsen recommends a second lavage if the first proves negative, but this has not been done except in a few cases.

ANALYSIS OF THE GROUP WITH NEGATIVE GASTRIC CONTENTS

Thirty-one cases, or 52.6 per cent of the 59 children studied, had negative gastric contents as shown by guinea-pig inoculation.

Age

The children with negative stomach contents as a group were older than those with positive findings. There were 29 per cent of the negative group under six years of age, while 50 per cent of the positive group were under six years.

Table of ages by years of children with negative gastric contents

Less than 1 year	1 case	6 years	4 cases
1 year	0 case	7 years	6 cases
2 years	0 case	8 years	4 cases
3 years	1 case	9 years	2 cases
4 years	2 cases	10 years	3 cases
5 years	5 cases	11 years	2 cases
		13 years	1 case

Total cases under 6 years ..... 9, or 29 per cent Total cases 6 years or over..... 22, or 70.9 per cent

Race

Miscellaneous:	White	18 cases or 58.0 per cent of the 31 cases
	Yellow	2 cases or 6.4 per cent of the 31 cases
	Mexican	6 cases or 19.3 per cent of the 31 cases
	Colored	5 cases or 16.0 per cent of the 31 cases

History of contact

Twenty-three of the 31 children, or 74.2 per cent, were contact cases. Eight children, or 25.8 per cent, had no history of known contact to tuberculosis.

The intracutaneous tuberculin test was positive in all of these children with negative gastric contents. All, with the exception of one, reacted to 0.1 mgm. of Old Tuberculin. One child reacted faintly to 1.0 mgm.

Classification of group on basis of roentgen examination

I: Parenchymal involvement. Only one of these cases was considered to have an active pulmonary lesion 5 cases; 16.1 per cent of 31 cases

II: Enlarged hilum without calcium. Of these six apparently have some involvement of the adjacent parenchyma..... 10 cases; 32.3 per cent of 31 cases
III: Calcium in parenchyma or in the regional lymph nodes..... 7 cases; 22.6 per cent of 31 cases
IV: No demonstrable lesion..... 9 cases; 29 per cent of 31 cases

ANALYSIS OF CASES WITH POSITIVE STOMACH CONTENTS

Twenty-eight, or 47.4 per cent of the 59 cases studied, had positive gastric contents. All cases of adult tuberculosis in children were excluded.

Nineteen of these children had an acute onset of their illness. Two of these had erythema nodosum. Five had what was diagnosed as pneumonia. Twelve of the nineteen with acute onsets had febrile reactions lasting from a few days to three months in one case. Cough was mentioned as a symptom at the onset of the illness of thirteen of the 28 children with positive gastric contents.

No history of acute onset could be obtained in nine, or 32 per cent, of the 28 cases. Seven of these nine, however, had some symptoms, such as malaise, cough or loss of weight. Two, *A. B.* and *G. S.* (see figure 3), were entirely without symptoms. Lesions were found on roentgen examinations made because of contact history.

The clinical course of all of these children has been favorable. The children of this group were either without expectoration, or the sputum was negative with the exception of 2 cases. These two developed pertussis, and with it had positive mouth sputum.

The weight-gain of these children was satisfactory, with the exception of *G. B.* He was fifteen months of age on admission and remained in the Sanatorium twenty-one months. He was 89 per cent of normal weight on admission and discharge. In spite of his lack of normal weight-gain his lung cleared nicely. Badly infected tonsils probably retarded his weight-gain.

Age

The children with stomach washings positive for tubercle bacilli have ranged from seven months to eleven years. If six years is considered school-age, 14 children, or 50 per cent, of the group of 28 were under school-age, and 50 per cent were of school-age. Should these children be allowed to attend public-school with healthy children? Several of them were physically able to carry on and would have been in school except for a consistent check on contact cases.

In explanation of this percentage of positive findings in children of school-age, it should be stated that 39 per cent of the 59 children studied were under school-age and 61 per cent of school-age.

Table of ages by years of children with positive gastric contents

Less than 1 year	1 case	6 years	5 cases
1 year	4 cases	7 years	1 case
2 years	3 cases	8 years	2 cases
3 years	2 cases	9 years	2 cases
4 years	2 cases	10 years	2 cases
5 years	2 cases	11 years	2 cases
Total under 5 years	14 cases or 50 per cent	Total over 6 years	14, or 50 per cent

Race

Miscellaneous:	White	13 cases, or 46.4 per cent of 28 cases
	Mexican	7 cases, or 25.0 per cent of 28 cases
	Colored	7 cases, or 25.0 per cent of 28 cases
	Hawaiian	1 case, or 3.6 per cent of 28 cases

Contact history

History of contact to open cases of tuberculosis was obtained in twenty-four out of the 28 cases, or in 86 per cent. No history of contact could be obtained in 4 cases, or 14 per cent.

Tuberculin test

The intracutaneous tuberculin test was positive in each of the twenty-eight children with positive stomach contents. The dosage of tuberculin was 0.1 mgm. or less.

Analysis of roentgen examinations

The roentgen examinations of all children with positive stomach contents have shown some evidence of pathological involvement. Some, however, have such minor lesions, or the lesions appear so well healed, that positive stomach contents were not expected. The 28 cases have been divided into three groups:

I:	Parenchymal involvement	15 cases, or 54 per cent of 28 cases
II:	Enlargement of the hilum or mediastinum with involvement of the adjacent parenchyma	8 cases, or 28 per cent of 28 cases
III:	Calcium in the parenchyma or regional lymph nodes, with or without demonstrable unhealed lesions	5 cases, or 18 per cent of 28 cases

Under parenchymal involvement, the cases with lesions predominately parenchymal have been grouped. All of these, except *G. R.* and *G. H.*, have also had enlargement of the hilar or mediastinal lymph nodes. Group II differs only in so far as the lymph-node involvement seems greater than the parenchymal involvement. In group III calcium has already been laid down either in the parenchyma or lymph nodes.

A comparative study of the roentgen examinations of the children with positive and the children with negative stomach contents is of interest. Out of the group of 59 children, nine were considered to have negative roentgenograms. These nine had negative stomach contents. Fifteen children classified as with parenchymal involvement had positive stomach contents, and five had negative findings. A total of 20 children fell in this group. Fifteen, or 75 per cent, had positive, and 5 cases, or 25 per cent, had negative stomach contents. Ten children with enlarged hilar or mediastinal lymph nodes had negative gastric contents. Eight children of a similar classification had positive gastric contents. Of the children that had demonstrable calcium in the roentgenogram at the time of the gastric lavage, 5 cases had positive and seven had negative stomach contents.

COMMENT

Inasmuch as children with pulmonary tuberculosis as a rule swallow their sputum, it is fairly safe to assume that tubercle bacilli in the gastric contents are from that source. There are, however, other possibilities. Tubercle bacilli may be ingested with food, especially raw milk. Tuberculosis of the stomach may exist, but it is a very rare condition; or, there may be a tuberculous process in the sinus, middle ear or tonsils.

Of these possibilities, tuberculosis of the tonsils has been considered the only source of error in our study. As far as could be determined by gross appearance, there were no cases of tuberculosis of the tonsils. Inasmuch as tuberculosis of the tonsil as a rule can be demonstrated only by study of the tissue-section, we have not ruled out this possibility. Since tonsillectomy is frequently done on these children during convalescence, tissue-section of the tonsils should be made in the future.

Tonsillectomy had been done prior to our study on 28.6 per cent of the children with positive gastric contents and on 55 per cent of the children with negative findings.

SUMMARY

1. Fifty-nine cases of childhood tuberculosis have been studied by gastric lavage and guinea-pig inoculation. All of these children reacted positively to the intracutaneous tuberculin test.

2. Fifty of the fifty-nine had demonstrable lesions in the roentgenograms of the lungs. Nine had no demonstrable lesions. Their only evidence of tuberculosis was the positive tuberculin test.

3. Twenty-eight cases, or 47.4 per cent, of the fifty-nine were found to have tubercle bacilli in the gastric contents. Thirty-one cases, or 52.6 per cent, of the 59 cases studied, were negative for tubercle bacilli in the gastric contents. Of the 50 children with demonstrable lesions, twenty-eight, of 56 per cent, had positive gastric contents.

4. Fourteen children, or 50 per cent of the cases with positive gastric contents, were of school-age. Should children with gastric contents containing tubercle bacilli be kept from close contact with healthy children?

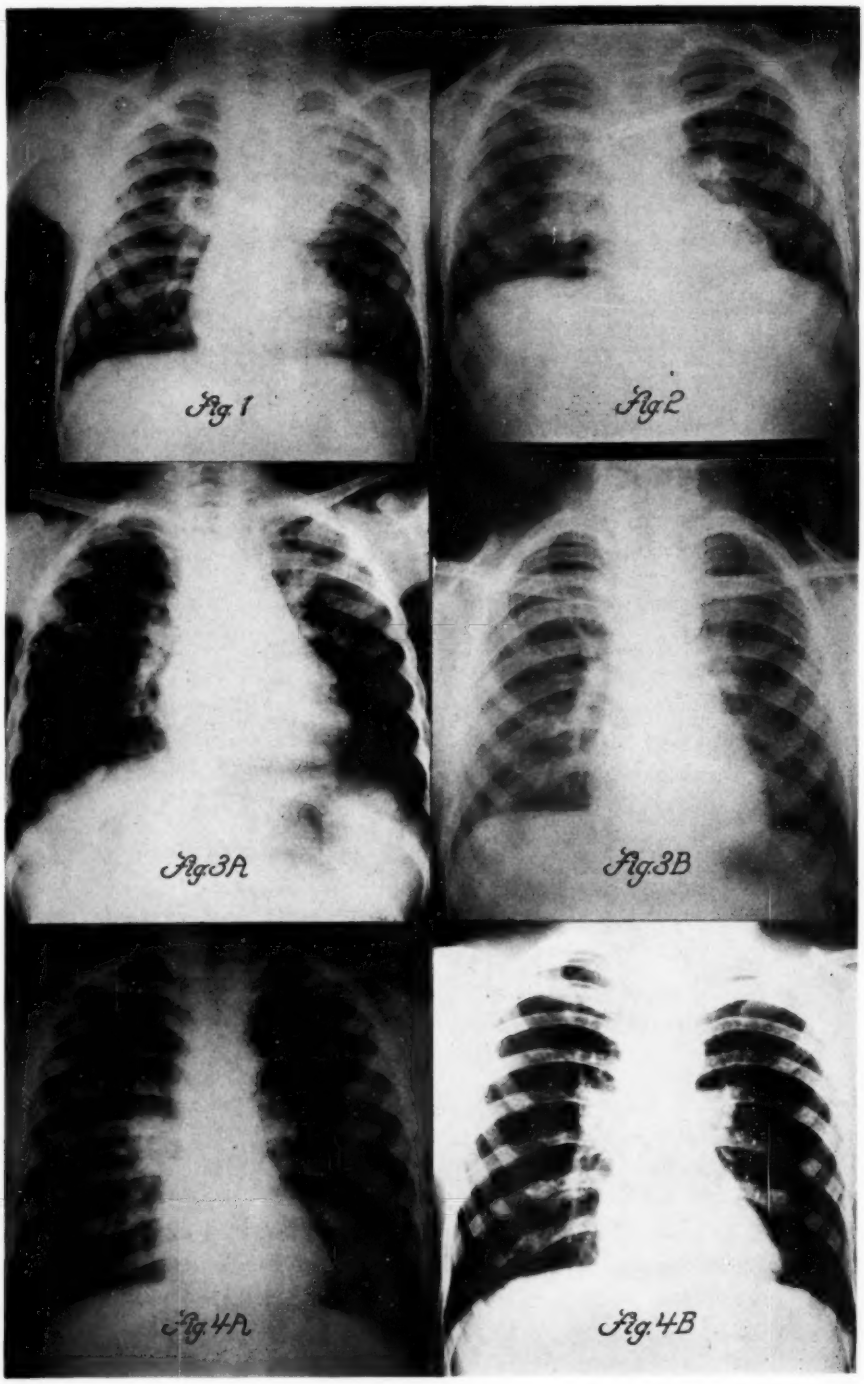
5. Twelve children had calcium in the parenchyma of the lungs or regional lymph nodes. Five of these had positive gastric contents.

6. Our study apparently indicates that all types of parenchymal lesions in childhood tuberculosis including the "C" group of McPhedran's classification are open cases. Further study is to be made before a definite conclusion can be reached.

Case Reviews

A. R., white boy, aged 6. Admitted May 16, 1932. For two years lived in contact with aunt who afterward died of tuberculosis. Present illness began March 14, 1932. High fever. Erythema nodosum. Fever subsided as nodules cleared. Temperature ranged from 100° to 104° for about ten days. Afebrile on admission to sanatorium. Weight 100 per cent normal. Intracutaneous tuberculin test positive Chest findings were negative on physical examination. Roentgen examination, March 22, 1932, showed enlargement of left hilum with apparently some involvement of adjacent parenchyma. Gastric lavage, June 2, positive for tubercle bacilli on direct smear after concentration. Roentgen examination, July 19, showed dense shadow occupying the upper third of left lung-field, and physical findings, impaired resonance over same area. Diminished breath-sounds; no râles. Course afebrile except for occasional fever to 100°. This apparently a typical case of epituberculosis. (See figure 1.)

W. S., white boy, aged 5. Admitted April 2, 1930. Often played in home where there was open case of tuberculosis. Erythema nodosum three weeks



FIGS. 1 TO 4

(For description see text)

before admission. Afebrile on admission. Intracutaneous test positive. Weight 88 per cent of normal. Impaired resonance over upper lobe, right lung. Breath-sounds high-pitched. No râles. Admission roentgenogram showed dense homogeneous shadow lateral to hilum and mediastinum on right. Guinea pigs inoculated November 1, 1930, and July 7, 1931, positive for tuberculosis. Roentgenogram, November 10, 1931, showed lesion largely cleared. Discharged January 18, 1932, in good clinical condition. (See figure 2.)

G. S., white boy, aged 8. Admitted June 5, 1931. Examined at clinic because of heavy contact with brother. Contact broken six weeks before the brother's death with pulmonary tuberculosis. Patient not ill. Past medical history negative, except for measles and mumps. Wieght 100 per cent of normal. Afebrile. Intracutaneous test, 0.1 mgm., 10 x 20 mm. at 48 hours. Physical examination revealed high-pitched breath-sounds over upper portion of left lung anteriorly. No râles at any time in twelve months' observation. X-ray series from April 30, 1931, to July 19, 1932. The first showed widening of mediastinum, especially on left, and infiltration of the parenchyma above level of third rib anteriorly; and the last, a little grayness of left apex and marked decrease in size of mediastinum. Clinical course entirely uneventful. Tonsillectomy, February 18, 1932, under general anaesthetic without untoward results. Guinea pig inoculated June 30, 1931, with gastric contents developed tuberculosis. (See figures 3A and 3B.)

R. B., white boy, aged 9. Admitted January 25, 1932. Contact to open tuberculosis at home, and examined because of this. He has, however, always been subject to respiratory infections. Three weeks before admission, developed fever of 102°; had fatigue and pain in right chest, and was in bed one week. Afebrile on admission. Weight 93 per cent of normal. Intracutaneous test positive. Chest examination not remarkable. Roentgenogram taken January 8, 1932, showed increased size and density of right hilum with apparently fibrous strand in parenchyma adjacent to hilum. Guinea pigs inoculated February 3, 1932, positive for tuberculosis. Clinical course uneventful. Afebrile. Good weight-gain. X-ray, September 10, 1932, showed decrease in size of hilum with disappearance of fibrous strand in parenchyma. (See figures 4A and 4B.)

Dr. Chesley Bush and Dr. C. V. Mason have given valuable assistance in this work.

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THE DEMONSTRATION OF TUBERCLE BACILLI IN THE SPUTUM, FAECES AND STOMACH CONTENTS OF TUBERCULOUS CHILDREN[1,2]

A Comparative Study

LUCY MISHULOW, CAMILLE KERESZTURI AND DAVID HAUPTMAN
Assisted by
MILDRED MELMAN AND MARIE ROMANO

The diagnosis of tuberculous infection in children is often difficult to establish; especially when the symptoms are indefinite and the only evidence of such infection is a positive tuberculin test. In most of these cases sputum is not obtainable, either because the children do not cough or because they are too young to bring up the sputum.

The question of a reliable laboratory method for making a diagnosis in such cases is still more or less debatable. The examination of faeces for acid-fast bacilli has not given uniformly favorable results in the hands of different workers.

Since the work of Meunier (1) on the examination of gastric contents for tubercle bacilli, an increasing number of workers have reported favorably on this method of diagnosis. Opitz, Poulsen, Delille, Friedländer and others[3] reported a fairly high percentage of positive results. Opitz and Poulsen recommended repeated examinations, as positive and negative results were obtained in the same cases when examined at different times. Delille used a special method of concentrating the gastric contents, which in his hands gave a much higher percentage of positives than the routine examination. The methods of examining the gastric contents differed with the various workers, for some employed smears and others cultures or guinea-pig inoculations. Opitz and Poulsen used all three methods.

We have reported more recently (2) the results of the examination of faeces and gastric contents in a group of 40 children. Faeces were examined at the Sea View Hospital in 25 of the 40 cases, and gave negative

[1] Read at the annual meeting of the American Public Health Association, October, 1932.

[2] This work was assisted by a donation by Mr. Howard Goodhart and was performed under the direction of Drs. W. H. Park and Bela Schick.

[3] For references see *Jour. Am. Med. Ass., May 28, 1932, xcviii, 1879–1881.*

results on routine smear examination. The gastric-lavage materials were examined at the Research Laboratories and were negative in all cases in that series on smear examination, but gave 17.5 per cent positive results on guinea-pig inoculation. In that series only one specimen of gastric contents was examined in each case; also the faeces were examined at different times from the gastric contents.

The present investigation was undertaken to study further some of the methods of diagnosis recommended, in order to determine their comparative value and to make a careful examination of the faeces when obtained at the same time as the gastric contents. It seemed to us that when tubercle bacilli are present in the gastric contents in sufficient numbers to be detected on smear examination, a considerable number of them should pass through the intestinal tract and appear in the faeces.

With this object in view, we examined a series of 60 cases. In order to control our technique, we included in this series some children who showed definite symptoms of tuberculous infection and were very ill at the time of examination. The other children were apparently well at the time of the examination, but some of them showed slight lesions on X-ray examination, while others showed no lesions and the only evidence of their having any tuberculous infection was a positive tuberculin test. We made no attempt to study any particular age-group. The children's ages ranged between 7 months and 15 years. Specimens of faeces and gastric contents were obtained in each case about the same time, usually on two successive days. Two specimens of stool and two of gastric contents were examined in most of the cases. In three cases we had three and in two cases four successive specimens of gastric contents. In 10 cases we were also able to obtain sputa at the same time as faeces and gastric contents. But, in the other cases, when sputa were obtainable, the examinations were made at different times, and therefore the results are not directly comparable.

The faeces were examined as follows: A heavy suspension of each specimen was treated with commercial antiformin until most of the organic matter was dissolved. We found that heating the mixture in a water-bath for 10 minutes at 45°C. gave satisfactory results. The specimens were then centrifugated for one hour at high speed, and smears were made of the sediment, stained by the Ziehl-Neelsen method, and examined with a mechanical stage for acid-fast bacilli.

The gastric lavage was done in the morning on an empty stomach, using 200 to 300 cc. of physiological saline solution. The specimens were al-

lowed to settle at room temperature for a short time, and smears were made of the sediment of each specimen and examined for acid-fast bacilli. If the result was negative on this preliminary examination, the specimens of the successive days were combined, and the entire amount centrifugated at high speed for one hour. The sediment was then divided into three parts: one was examined in the routine manner, by making smears after centrifugation; the second was examined by Delille's method; and, if the results were negative on all smear examinations, the third part was inoculated subcutaneously into guinea pigs.

To facilitate the tabulation, we divided the children in this series into three general groups: Those in group A were apparently well at the time of examination: they gained weight, had no elevation of temperature and no cough, but were Mantoux-positive; and, while some showed pathological X-ray signs, others did not. The children in group B were definitely, but not severely ill; and those in group C were very ill.

The results obtained in this investigation are briefly as follows:

In the 60 cases studied, the faeces were positive in 12 and the gastric contents in 16 cases. In one case the faeces was positive and the gastric contents negative. This gave a total of 17[4] positive cases on smear examination.

Table 1 gives the results of these 17 cases and shows the comparative value of the methods employed.

Table 1 shows that there was a considerable difference in the results obtained in the specimen taken on different days,—ranging from positive to negative or only weakly positive. This is in accord with the work of Opitz and of Poulsen and shows the necessity of making repeated examinations if the result is negative.

Eleven cases gave positive results on both faeces and gastric-lavage examination and, when sputum was examined, it was also positive in these cases. One case was positive on the faeces and negative on gastric lavage, and 5 cases were positive on gastric lavage and negative on faeces examination. The result therefore seems to be in favor of gastric-contents examination. But we made more examinations of the gastric contents than of the faeces, since we used Delille's method in addition to the routine examination. Also, one of the 5 positive cases of gastric contents which were negative on faeces examination had so few acid-fast bacilli that these were only found after prolonged search on reëxamina-

[4] One of these cases had so few acid-fast bacilli in the gastric contents that they were found only when the smears were reëxamined after the guinea pigs proved to be positive.

TABLE 1

Comparative study of the presence of tubercle bacilli in faeces, gastric contents and sputum in tuberculous children

CASE	CLINICAL DIAGNOSIS	AVERAGE TEMPERATURE	GROUP	LABORATORY EXAMINATIONS					SPUTUM
				Specimen	Faeces	Gastric contents: Smear unconcentrated	Gastric contents: Smear concentrated	Gastric contents: Delille method	
1. S. P.	Destructive tuberculosis right u. l.; productive tuberculosis whole left and right l. l.; 12 years old.	<101°	C	I II III	+ +	+ ++ +	→ +	+	1 × negative 5 × positive
3. H. G.	Proliferative tuberculosis r. l. l.; destructive tuberculosis whole r. u. l.; 5½ years old.	<100°	C	I II III	+ (few) + (few)	+1 ++ + (few)	→++	+	7 × positive
5. R. F.	Destructive tuberculosis l. u. l.; 7⅔ years old.	101°	C	I II	+	+ (few) No smear	+	++	3 × positive
8. F. P.	Destructive tuberculosis whole left lung; 12⅔ years old.	100°	C	I II	+ (few) + (few)	+ Negative	→Negative	Negative	8 × positive
9. F. L.	Bilateral destructive tuberculosis; 7 years old.	102°	C	I II	+ ++	+ ++	→ ++	+1	4 × negative 7 × positive
10. S. Z.	Destructive bilateral tuberculosis; diabetes mellitus; 13 years old.	101°	C	I II	+ (few)	+ (few) Negative	+	+	3 × positive 2 × negative
27. G. Z	Destructive tuberculosis l. l. l.; 11 years old.	<100°	B	I II	+ (few) +	+ + (few)			No sputum
28. A. diS.	Destructive tuberculosis right m. l.; 12 years old.	<100°	B	I II	+ (few) + (few)	Negative Negative	+		4 × positive

29. E. T.	Destructive bilateral tuberculosis; 12 years old.	101–103°	C	I II	+ (few) + (few)	+ + (few)			3 × positive 2 × negative
53. R. Simone	Destructive proliferative tuberculosis, both lungs; 10 years old.	<101°	C	I	+	+			1 × positive
54. R. Saul.	Productive tuberculosis right lung; 7 years old.	<101°	C	I II	Negative + (few)	Negative + (few)			No sputum
14. H. C.	Destructive tuberculous infiltration of whole right u. l.; questionable tuberculosis of frontal bone; 8 months old.	101°	C	I II	Negative + (few)	Negative Negative	Negative	Negative	No sputum
45. E. A.	Destructive tuberculosis, left upper lobe; 10 years old.	<100°	B	I II	Negative Negative	Negative + (few)			5 × negative 1 × positive
6. A. D.	Destructive tuberculosis, left lung; 6½ years old.	101–102°	C	I II	Negative	Negative → + (few) + (few)	+ (few)	+ (few)	7 × positive
36. B. S.	Proliferative tuberculosis, bilateral; 15 years old.	<100°	A	I	Negative	Negative → + (few)	+ (few)	+ (few)	No sputum
41. M. L.	Destructive tuberculosis r. u. l.; tuberculosis, left hip; 14 years old.	<100°	B	I II	Negative	Negative Negative	+ (few)		2 × negative 2 × positive
46. S. S.	Partial pneumothorax right lung; pleurisy with effusion (rt.); atelectasis, right upper lobe; 6 years old.	<100°	C	I II	Negative Negative	Negative Negative	+ few*	+ few*	2 × negative

* Positive on reëxamination.

++: acid-fast bacilli numerous.

+ 1: acid-fast bacilli fairly numerous.

+: acid-fast bacilli easily found.

tion of the smears, and in 2 cases we obtained only one specimen of faeces and two of gastric contents. If we had examined 2 specimens of faeces we might have obtained positive results for the faeces as well.

Delille's method was used in the examination of gastric contents in 53 cases. In none was a positive result obtained by his method when it was negative on the routine-smear examination.

The specimens of gastric contents of the 45[5] cases that were negative on all smear examinations were inoculated into guinea pigs and gave the following results: In 11 cases the guinea pigs died of other infections within one to three weeks after inoculation. None of them showed any tuberculous lesions: however, since the period of incubation was so short a negative result has no significance.

The guinea pigs inoculated with the remaining 34 specimens survived from one to three months, and gave five 5 positive and 29 negative results. In four of the 5 positive cases, the guinea pigs were killed after 64 to 75 days, and in every case the tuberculous lesions were local, that is, in the inguinal and peritoneal lymph nodes. Thus the tubercle bacilli in these specimens must have been very few. The guinea pigs in the fifth case showed generalized tuberculosis after 35 to 44 days and, when the original smears of the specimen were reëxamined, the bacilli were also found in the smears.

The 17 cases tabulated here show that there were 12 (20 per cent) positive on faeces and 16 (26.6 per cent) on gastric-contents smear examinations, with an additional 4 cases positive on guinea-pig inoculation. This makes a total of 20 positive cases by gastric-contents examination, or 33⅓ per cent. Since the faeces were not examined by guinea-pig inoculation a direct comparison of the two methods cannot be made.

If we consider the total number of positive results obtained in this investigation, irrespective of the type or degree of infection or the method of examination, positive results were obtained in 21 of the 60 cases, or 35 per cent. If, however, we consider the results with reference to the different groups *A*, *B* or *C*, the results are as appear in table 2.

The results in table 2 show that in 30 cases of group A the faeces were negative, and the gastric contents positive in 1 case on smear and 2 cases on guinea-pig inoculation, or a total of 10 per cent positive.

In 11 cases of group B the faeces were positive in 2 cases and the gastric contents positive in 4 cases, with an additional 2 cases positive on guinea-pig inoculation, giving a total of 6 positive cases, or 54.5 per cent.

[5] One of these cases was found to be positive on reëxamination of the smears.

TABLE 2

Results of the examination of faeces and gastric contents for tubercle bacilli in three clinically different groups of tuberculous children

Group A: Children who were apparently well: 30 cases

NUMBER OF CASES	FAECES	GASTRIC CONTENTS			AGE
		Direct	Concentrated	Guinea pigs	
1	−	−	+ few	−	15 years
2	−	−	−	+	7 months and 4 years
7	−	−	−	0	1½ to 5 years
20	−	−	−	−	9 months to 14 years

Positive faeces: none.
Positive gastric-lavage smears: 1 case (3.3 per cent).
Total positive gastric-lavage smears and guinea pigs: 3 cases (10 per cent).

Group B: Children slightly ill: 11 cases

1	+	+		Not done	11 years
1	+ few	−	+	Not done	12 years
1	−	+ few		Not done	10 years
1*	−	−	+ few	Not done	14 years
2	−	−	−	+	2½ and 4 years
1	−	−	−	0	9 years
4	−	−	−	−	10 months to 11 years

Positive faeces: 2 cases (18.1 per cent).
Positive gastric-lavage smears: 4 cases (36.3 per cent).
Total positive gastric-lavage smears and guinea pigs: 6 cases (54.5 per cent).
Total positive cases: 6 cases (54.5 per cent).

Group C: Children who were very ill: 19 cases

9	+	+		Not done	5½ to 13 years
1	+	−	−	0	8 months
1*	−	+		Not done	6½ years
1	−	−	+† few	+	6 years
2	−	−	−	0	3 and 6½ years
5	−	−	−	−	15 months to 11 years

Positive faeces: 10 cases (52.6 per cent).
Positive gastric-lavage smears: 11 cases (57.8 per cent).
Total positive gastric-lavage smears and guinea pigs: 11 cases (57.8 per cent).
Total positive cases: 12 (63.1 per cent).

Groups A and B: 41 cases: positive = 9 cases (21.9 per cent).
* Only one specimen of faeces and two of gastric contents.
† = positive on reëxamination.
+ = positive; − = negative.
0 = guinea pigs died in less than one month after inoculation.

In the 19 cases of group C, faeces were positive in 10 cases and gastric contents in eleven, with a total number of 12 positive cases, or a total of 63.1 per cent. In this group the examination of faeces and gastric contents by smear gave practically equally satisfactory results.

In two of the 5 cases that were positive on gastric lavage and negative on faeces or smear examination, there was only one specimen of faeces examined, as compared with two of gastric contents. Possibly if 2 specimens of faeces were examined in those cases, the results might have been the same in both.

The classification of the cases into the above three groups was made on the basis of the children's general health and not on clinical and X-ray diagnosis, and independently of the laboratory findings and of their age. The

TABLE 3

Frequency of positive findings in faeces or gastric contents according to type of tuberculosis

TYPE OF CASE	TOTAL NUMBER	POSITIVE	NEGATIVE	PER CENT OF POSITIVE
Parenchymatous destructive pulmonary tuberculosis	18	15	3	83.3
Parenchymatous nondestructive pulmonary tuberculosis	25	6	19	24
Hilum lymph-node tuberculosis or only positive intracutaneous test	10	—	10	0
Tuberculous pleurisy with effusion	2	—	2	0
Bone tuberculosis	1	—	1	0
Tuberculous peritonitis	4	—	4	0

laboratory results correspond very closely with this classification, as the highest percentage of positive results was obtained in group C and the next higher in group B, both obviously active cases.

If the results of groups A and B are considered together, which gives a group of 41 cases, the result is a total of 9 positive cases, or 21.9 per cent. This gives a somewhat higher percentage of positives than we obtained in our previous study of 40 cases (17.5 per cent).

If we classify the cases according to the type of tuberculosis, the results are as in table 3.

The highest percentage of positive results was obtained in the cases of destructive pulmonary tuberculosis, which in the majority of the cases corresponds with the previous classification on the basis of the general health of the children.

SUMMARY

1. A comparative study was made of faeces, stomach contents, and in some cases of sputum, for the presence of acid-fast bacilli in 60 cases of tuberculous children. Twelve cases of faeces (20 per cent) and 16 of gastric contents (26.6 per cent) were positive on smear examination. Eleven of these were positive for both faeces and gastric contents; one was positive for faeces only; and five were positive on gastric lavage only. In two of the 5 latter cases, only one specimen of faeces and two of gastric contents were examined, and in one the acid-fast bacilli were so few in number that they were found only after prolonged search on reëxamination of the smears.

2. Of 44 gastric-lavage specimens that were negative on all smear examinations, four were positive on guinea-pig inoculation. This gave a total of 20 cases, or 33⅓ per cent positive results on gastric-lavage examination by smears and guinea-pig inoculation. Since the faeces were not examined by guinea-pig inoculation, a direct comparison of the two methods in percentages cannot be made.

3. Delille's method was tested on 53 specimens obtained by gastric lavage. In no instance was a positive result obtained by his method when a negative result was obtained by the routine concentration method.

4. The results of sputum examination, when sputum was available, corresponded closely to the gastric-lavage results.

CONCLUSIONS

From the results obtained in this investigation, the following conclusions may be drawn:

1. Guinea-pig inoculation should be made as a final confirmation when specimens are negative on smear examination.

2. Repeated examinations should be made in doubtful cases, inasmuch as positive and negative results are frequently obtained in the same case when the specimens are taken on different days.

3. The indications are that repeated examinations of faeces by smear and guinea-pig inoculation may prove as satisfactory as the examination of gastric-lavage specimens.

4. As a diagnostic method, the examination of faeces would be much more desirable than gastric lavage, as it could be easily repeated as often as necessary without any discomfort to the patient. Although gastric-lavage examination has given very satisfactory results it is not always a desirable procedure, as it is hard on the patient when repeated examina-

tions are made, and it is not feasible in some cases, especially when the patient is not hospitalized.

5. In the 60 cases in this series, the examination of faeces, gastric contents, and sputa (when they were obtained) showed 10 per cent positive in children who were apparently well at the time of examination, 54.5 per cent positive in those that were slightly ill, and 63.1 per cent positive in the children who were very ill.

6. Of the children who had destructive parenchymatous pulmonary lesions, 83.3 per cent showed positive results and of those who had nondestructive parenchymatous lesions, 24 per cent were positive. Cases with only positive intracutaneous tests, hilum lymph-node tuberculosis, pleurisy with effusion, and tuberculous peritonitis, were all negative.

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TUBERCLE BACILLI IN THE SPUTUM AND FAECES OF CHILDREN WITHOUT PULMONARY TUBERCULOSIS[1]

J. P. NALBANT

During the last few years several investigators have reported some interesting findings in the field of childhood tuberculosis, and all have advanced more or less different theories as to the meaning of the results obtained. These findings have been concerned with tubercle bacilli discovered in the gastrointestinal tracts of children. Some of these workers have investigated the faeces, others have examined the gastric contents, the bile and the blood, and some have searched the sputum for the tubercle bacilli. They all have reported surprisingly high percentages of positive findings among the children subjected to their investigations.

It is not surprising that tubercle bacilli should be found in the faeces, gastric contents or sputum of children with manifest pulmonary tuberculosis. Such bacteria are easily demonstrable by culture or guinea-pig inoculation. However, their presence in these bodily products of children who have no roentgenological or physical signs of pulmonary tuberculosis is truly surprising. This observation has been made a number of times and we consider it as important from both clinical and epidemiological standpoints.

Apparently Munier was the first person to suggest the examination of gastric contents for tubercle bacilli. This was in 1898. In 1927 Armand-Delille (1) reported that he had found tubercle bacilli in the stomach contents of 31 per cent of children who were considered only as suspects and whose roentgenograms were practically normal. His method consisted of the introduction of about 80 cc. of water into the stomach, and, after withdrawal, of its examination for tubercle bacilli. Poulsen (2) examined similarly the gastric contents of 62 suspected children under three years of age and found that 41 showed tubercle bacilli. He also examined 48 cases over three years of age and found bacilli in twelve. He advocated gastric lavage on two counts: first, because of the necessity of accurate diagnosis, in order to institute intelligent treatment, and, second, because of the fact that the sputum is usually unobtainable in

[1] From the William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

infants and small children. Again, a preliminary report by Kereszturi, Schick and Mishulow (3) dealt with a group of 40 children, of whom 21 had no demonstrable pulmonary lesions. Seven of the 21 showed tubercle bacilli in their gastric contents. Of the seven, four were from children with no thoracic disease whatever; the remaining three had spondylitis, phlyctenular conjunctivitis and pleurisy without demonstrable pulmonary involvement.

Opitz (4) reported his study on a similar group. Of a total of 47 examinations of gastric contents of children, 14 contained tubercle bacilli. His 47 cases included seven with mediastinal pleurisy of which one was positive; 24 with increased root shadows, three positive; three with cervical lymphadenitis, one positive; six bone-and-joint cases, two positive; seven cases of meningitis, seven positive.

Our own observations have been interesting. Out of a total of 72 cultures and guinea-pig inoculations from faeces and sputum of 65 children under 15 years, we have found 24 cases which showed tubercle bacilli beyond any doubt. Of the 65 cases, 19 were from children whose physical examination and X-ray studies revealed no demonstrable parenchymal lesions and who were considered negative so far as the lungs were concerned. Of these, seven showed tubercle bacilli in their sputum or faeces. The 7 cases that gave positive cultures or guinea-pig inoculations consisted of one with fibrinous pleurisy, two with definitely enlarged tracheobronchial lymph nodes, four with no demonstrable enlargement of the lymph nodes and no demonstrable infiltrations in the lung. The remaining 17 positives were from children who had the childhood type of tuberculosis with demonstrable parenchymal infiltration in the lung.

If we may summarize the results as reported in the literature, along with our observations here, the resulting figures are astounding and unusually significant. Out of a total of 197 children with no pulmonary tuberculosis, including cases of bone-and-joint tuberculosis and tuberculous meningitis, 81 showed tubercle bacilli in their gastric contents or faeces. This means that 41 per cent of the children examined showed evidence of a tuberculous infection that was probably active.

The various methods, advocated by different workers for the detection of the tubercle bacilli, are based largely upon the assumption that the child swallows sputum, which an adult would expectorate. Whether the material examined be faeces or gastric contents obtained by lavage, the results should be the same. Experience has taught us to believe that repeated examinations of the stool will yield as high a percentage of posi-

tive results as will gastric analysis. The former procedure is certainly easier on the patient and the physician.

The significance of the presence of tubercle bacilli in the gastrointestinal tract of children is what we wish to emphasize most at this time. In order to do this, it is important to find the source of these bacilli. Some of the possible sources are the following:

1: A tuberculous infiltration in the lung. Naturally, sputum containing tubercle bacilli, brought to the pharynx by cough or the ciliary action of the lining of the bronchi and trachea, may be swallowed. This source is quite evident in cases in which there is a demonstrable lesion in the lung.

2: A receding type of childhood tuberculosis in which the parenchymal lesion may have cleared roentgenologically but not pathologically.

3: The next important source may be a caseated tracheobronchial lymph node which may break into the trachea or a bronchiole and its contents be expectorated or swallowed. This is quite possible, as cases of this sort are occasionally seen at autopsy. A lymph node may even penetrate the oesophagus and its contents may be discharged into it.

4: Krause, Frankl, Mikulowski (5) and others believe that the bacilli present in the faeces may originate from infected bile. They found tubercle bacilli in the bile of a large proportion of cases of tuberculosis in man and in animals. Although one can conceive of the presence of tubercle bacilli in the bile of individuals with advanced pulmonary tuberculosis, it would be quite far-fetched to think that children with no generalized tuberculosis (without sufficient lesion in the lung to be seen in the X-ray) would have tubercle bacilli in the bile unless it be assumed that the gall-bladder be the primary seat of the infection, which is not probable.

5: Tuberculous enteritis or gastritis. These are quite uncommon in children, especially in nonpulmonary cases. A broken-down tuberculous lymph node in the abdomen may be suspected in such circumstances.

6: The possibility of an upper respiratory infection with the tubercle bacillus,—possibly a tuberculous otitis media or tuberculous sinusitis, or tubercles in the tonsils,—may be thought of. However, these are not common enough to give the high percentage of positive cases we have seen in the above summary.

7: The presence of a tuberculous growth in a bronchus or a bronchiole, —a tuberculoma of the bronchial structure which could shed bacilli from its ulcerated surface into the bronchus and be expectorated,—is also a possibility.

Out of the above seven possibilities as sources of the bacilli, number 2, namely, a receding childhood type of parenchymal infiltration which has cleared roentgenologically yet not completely rid of the bacilli, and number 3, namely, the breaking down of a tuberculous tracheobronchial lymph node and the emptying of its contents into the bronchus for eventual swallowing, seem to be the most probable ones. Yet the advocates of the bile theory think that contaminated bile may be regurgitated into the stomach. Is it possible for bacilli to be circulating in the bloodstream of these children and somehow to be excreted into the gastrointestinal tract without causing generalized tuberculosis or meningitis? Yet the great majority of instances of Pott's disease, of tuberculous bone-and-joint disease, and of tuberculous pleurisy may very well be localizations of a former bacillaemia. Many other questions come up in this connection which will necessitate further investigation before they can be answered.

What is the clinical and social significance of the results of this study? No doubt a child with tubercle bacilli in its stools or stomach contents should be considered as a menace to other uninfected children. They should be isolated in sanatoria and be treated as tuberculous even though the source of the bacilli may not be evident. They should have the contents of their gastrointestinal tract repeatedly cultured and should not be considered safe to be with other children until they are free from the bacilli. They are themselves in danger of developing fresh lesions in their lungs or elsewhere, thus making their prognosis more serious.

CONCLUSIONS

1. Out of 19 children under fifteen years of age, seven were found to have tubercle bacilli in the contents of their gastrointestinal tract. They had no demonstrable pulmonary tuberculosis.

2. The clinical and social significance of the results of the investigation was discussed.

The above report, we hope, will stimulate a renewed and greater interest in this line of work. Later, we hope to be able to report a more complete and more extensive analysis of a larger number of cases.

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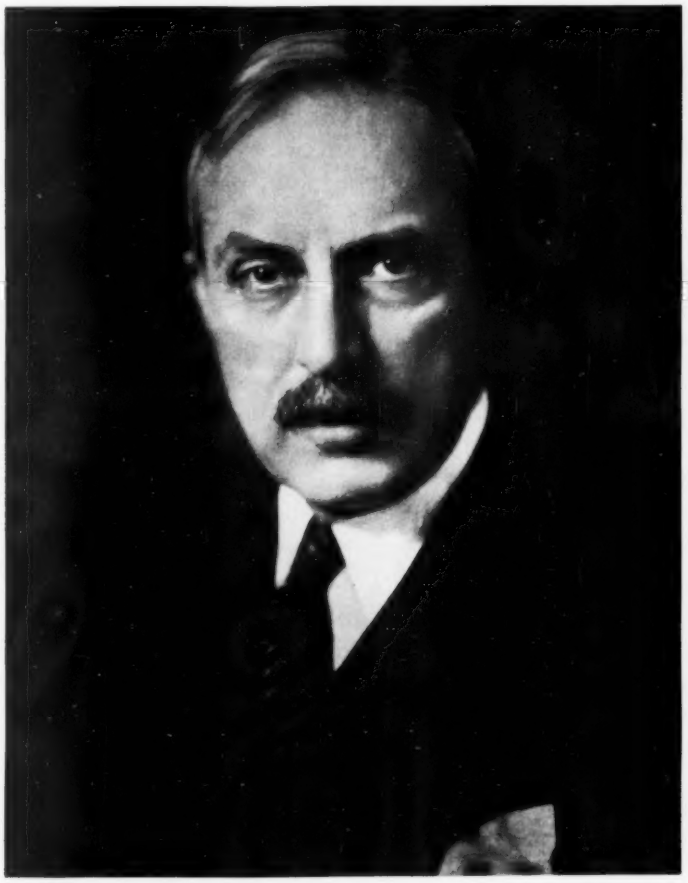
Linsly Rudd Williams
1875—1934

The cause of public health and the antituberculosis movement have lost a powerful exponent in the death of Dr. Linsly R. Williams which occurred on January 8, 1934.



Dr. Williams's notable career in the field of social and preventive medicine was based upon a training and experience which were extraordinarily varied.

Starting his medical career as a clinician of outstanding ability he soon became interested in the social implications of medicine and became a guiding factor in the medical aspects of the work of the Association for Improving the Condition of the Poor in New York City.

His capacities were recognized by the late Dr. Hermann M. Biggs who persuaded Dr. Williams to enter the public-health field and appointed him Deputy State Commissioner of Health of New York State in 1914. Ever since that time Dr. Williams devoted his life to the public rather than the private practice of medicine.

During the War he served in France as Lieutenant-Colonel assigned to sanitation in the Medical Reserve Corps, and after the armistice he succeeded Dr. Livingston Farrand as Director of the Rockefeller Tuberculosis Commission in France, whose work has exerted a notable influence upon preventive medicine in France.

Upon his return to America in 1922 he became Managing Director of the National Tuberculosis Association in which capacity his experience and unusual administrative ability did much to strengthen the position of the Association as one of the outstanding voluntary health organizations of the country.

When the New York Academy of Medicine reorganized and extended its activities in 1924 Dr. Williams was called to be its Director, dividing his abundant energies between the two organizations for four years, until in 1928, when he resigned from the National Tuberculosis Association and became the full-time Director of the Academy of Medicine which he served with outstanding success until his death.

In 1922 he was elected President of the National Tuberculosis Association and in 1928 President of the New York Tuberculosis and Health Association, which position he also retained during his life-time.

In addition to these regular major activities Dr. Williams served the community notably in many allied fields. He was a Director and member of the Technical Board of the Milbank Memorial Fund and also a Director of the Bellevue-Yorkville Health Demonstration. He was a member of the Board of Managers of the Association for Improving the Condition of the Poor and of the Tuberculosis Committee of the State Charities Aid Association.

He was deeply interested in the promotion of medical education and, through his position as Director of the Academy and as Trustee of Columbia University, he did much to promote the cause of better training for both undergraduate and postgraduate medical students.

There were few activities in the fields of public health, preventive medicine and social welfare, whether local, state or national, in which his wise counsel was not eagerly sought and always unsparingly given.

In international health activities, particularly those of France, he was also deeply concerned and the French Government recognized his services by three times awarding him decorations in the Legion of Honor.

The going-out of such a full life leaves a great gap which cannot be filled. The whole cause of public health to which he devoted his unusual talents and abilities has suffered an irreparable loss. His achievements will, however, leave an enduring record in the health annals of our country and will constitute a permanent monument to his memory.

With such a variety of interests in his full life it was inevitable that Dr. Williams's personal contacts should be extraordinarily numerous.

Combined with an ability and experience of a very high order were his rare personal qualities. His energy was untiring, his enthusiasm contagious. With a quick appreciation of human needs and interests was combined a clarity of judgment and a persuasiveness of manner which gave him great power. His quiet demeanor, his rare sense of humor and his courageous devotion to the highest ideals of honor and of service commanded the greatest respect and the deepest affection of all with whom he came in contact, so that, notwithstanding the notable achievements of his life, it is in the hearts of his host of friends that the most enduring monument to his memory will rest.

A rare soul as well as an outstanding leader has been lost to us. Consequently we are all bowed in deep sorrow.

JAMES ALEXANDER MILLER.

HAEMATOGENOUS PULMONARY TUBERCULOSIS[1]

JAMES ALEXANDER MILLER

INTRODUCTION

The prevailing clinical classification of pulmonary tuberculosis, together with the concept that the disease is of local exogenous and bronchogenic origin, with extension by bronchogenic spread, has failed to explain the extraordinary pleomorphism of chronic pulmonary tuberculosis as we know it to-day.

A more reasonable basis for a better understanding of the many puzzling problems which confront us in the study of chronic pulmonary tuberculosis is afforded by the concept of haematogenous origin of many forms of the disease, a concept which has indeed always prevailed in the French literature and has come also to be accepted to a great extent in recent German literature.

In fact, at the present time a great body of bacteriological, immunobiological, biological and clinical evidence in favor of chronic haematogenous pulmonary tuberculosis has accumulated in the international literature, while this aspect of phthisiology has been largely neglected in this country.

Without questioning the pathological and clinical importance of the concept of localized bronchogenic phthisis, it would appear timely to call attention, also in the American literature, to the evidence of existence of haematogenous forms of chronic pulmonary tuberculosis. At the same time it will be necessary to point out that the entrance of this new concept into our clinical and pathological thinking must profoundly affect our ideas of the epidemiology and pathogenesis of pulmonary tuberculosis in general.

While undertaking the introduction into American literature of the concept of chronic haematogenous pulmonary tuberculosis, the writer is fully aware that the subject is by no means entirely proved and that there are many gaps in the evidence. Hence, the clinical pictures here to be

[1] From the Tuberculosis Service of Bellevue Hospital, New York City. Presented at a session of the Clinical Section at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 30, 1933.

discussed, as representing various phases of haematogenous chronic pulmonary tuberculosis, should not be taken in any sense as final clinical entities. Future wider experiences made in the light of the new concept must be awaited before definite types of chronic haematogenous pulmonary tuberculosis can be crystallized out. It is emphasized, however, that if such experience establishes beyond reasonable doubt the existence of distinct types of haematogenous chronic pulmonary tuberculosis our ideas of both preventive and curative treatment of a vast proportion of our cases of chronic pulmonary tuberculosis may be profoundly modified.

1. THE PAST AND THE PRESENT CONCEPT OF TUBERCULOSIS AS A SYSTEMIC INFECTION

Following as the concept of chronic haematogenous tuberculosis does from the broader one of tuberculosis as a systemic infection, it will aid our understanding to review here the evolution of this concept up to the present time.

Upon the discovery of the infectious nature of pulmonary tuberculosis the systemic character of the infection was at first taken for granted. To the well-known and obviously systemic miliary form of the disease, Landouzy (1) soon added the entity of *typho-bacillose*, which was perhaps the earliest recognized cryptic blood-borne tuberculous disease. Then Poncet and Leriche (2) described their *tuberculose inflammatoire*, which represented in a definite form the mild generalized conditions which stamped tuberculosis as the focal infection of our modern concepts, with its fleeting, insidious and protracted course, manifesting itself in the form of polyserositis or similar rheumatoid processes, and also in the form of abortive pulmonary lesions.

The French clinical genius was at its best in the admirable classification of pulmonary tuberculosis by Bard (3) (1901) and Piéry (4) (1910), which achieved the integration of the anatomical and clinical data then available, and was based upon the fundamental idea that pulmonary tuberculosis is a part of a generalized tuberculous infection. Their classification of pulmonary tuberculosis includes the *granulies* of varying clinical acuteness, as well as the *granulies* of the less acute and subchronic type, and the chronic *granulie discrète*, the *tuberculosis fibrosa densa* representing apical residues of a one-time mild dissemination, the *phthisis fibrosa densa* and *diffusa* as manifestations of a generalized disseminated pulmonary tuberculosis tending to localization. These various pulmonary

processes were interpreted as an expression of the range of transition from the most severe, overwhelming, to chronic insidious or abortive disease.

The construction of the natural history of tuberculous infection on the basis of pathologicoanatomical and immunobiological facts was first attempted more than a generation ago by Petruschky (5), and after him by Hamburger (6), but was achieved first on an extended scale by Ranke (7) (1916). In Ranke's system the tuberculous infection appears for the first time as a logical biological sequence of events, well-grounded upon the integration of the vast amount of pathological, clinical and experimental data then available. Ranke's three-stage system of tuberculosis was probably constructed upon the analogy of the cyclic evolution of syphilitic infection, but in reality is based upon a broader principle, namely, the natural history of all infectious diseases in general, as embodied in our modern concepts of infection to be discussed later. The principle of relative incompatibility between generalization and localization forms of the infection,—although it was known and was pointed out by clinicians repeatedly since Ferran (8) as applying to tuberculosis,—was also first set down in definite terms by Ranke (7).

In building up his three-stage system of tuberculosis Ranke was rather engrossed in the effort of fitting the pathological and immunobiological facts into a logical sequence of events. While Ranke (7) indicated in broad outlines the manifold clinical pictures forming the transition from the primary complex, through generalization, to chronic isolated phthisis, it was left to Wilhelm Neumann (9) to blend the ingenious classification of Bard (3) and Piéry (4) with the erudite system of Ranke (7). With the work of Neumann (9), and with the additional contributions by a great number of recent workers, the harmonious coördination of the clinical kaleidoscopy and the biological sequence of tuberculous infections was finally achieved.

As a result of this work it is possible now to arrange the vast polymorphism of tuberculosis in an easily reviewable order, showing the range of clinicopathological conditions from the simple abortive primary complex, through mild and increasingly severe, to overwhelming generalization, and from mild abortive apical lung lesions to hyperacute extensive multilobar localizing processes.

The concept of tuberculosis as a systemic disease, which has thus been evolved, is entirely analogous to the behavior of other bacterial diseases. In most bacterial infections there is an initial lesion at the point of

bacterial implantation, with a local sensitization and an increased capacity of the cells to react to the invading microörganisms. After that there follows a period of generalization in which the bacteria are multiplied in the tissues and invade the blood-stream. Toward the end of this period a general destruction of the bacteria takes place. Finally, after the bacteria have disappeared from the blood, local lesions appear in various parts of the body, corresponding to points of diminished resistance, where the bacteria have settled down.

Accordingly, in every bacterial infection we observe clinical forms showing fluent transitions from hyperacute generalized infection without evidence of localizing phenomena, on one end, and the final strictly localized process, on the other. Generalization and localization coexist rather infrequently; they are to some extent incompatible in the sense that, while generalization prevails, localization is in abeyance or is present only in imperfect form (this is the principle of incompatibility alluded to above).

In very chronic infections there exists usually a period of overlapping of localization upon generalization, with the latter already in abeyance while the former is in ascendency. The various possibilities of reinfection and secondary infection will also tend to fuse, more or less, these infectious periods into one another, so that their border-lines will become indistinct.

The so-called focal infections with which we are all familiar represent a chronic mild type of generalization with repeated short exacerbations showing little tendency to localization.

These features of general bacterial diseases found their counterpart in tuberculosis, as already indicated above. Representing, as tuberculosis does, a typical chronic infection, and considering the extraordinary opportunities afforded in it for reinfection and superinfection, it must be expected that the various phases of the infection should become frequently fused and obscured. However, taken as a whole, tuberculosis should not behave differently from other infections; namely, we must expect here too clinical forms representing every form between overwhelmingly generalized and strictly localized disease, both showing variations in acuteness and in chronicity. We should also expect forms of tuberculosis simulating insidious focal infection.

In the clinical section of this paper an attempt will be made to show that just such is the case. Suffice it here to establish the fact that tuberculosis behaves in general as do other bacterial infections. However, in apparent contrast to other bacterial disease, the bacteriological evidence

of the systemic nature of tuberculous infection is not as constant as one should expect.

As Wilson (10) very recently concluded:

> Tuberculous bacillemia is of far less frequent occurrence than has been claimed by many workers. It would appear that bacillemia of an intensity sufficient to be detected by our present methods of examination, is, except as a transitory phenomenon, rarely present in tuberculosis until the disease has assumed a more or less acute phase accompanied by extensive lesions or by actual generalization. While rare in the early stages of pulmonary and non-pulmonary tuberculosis, it may be present in perhaps as many as 5–10 per cent of severe advanced and progressive cases of pulmonary, and in 30–40 per cent of cases of miliary tuberculosis. In the post mortem heart blood of patients who have died of tuberculosis, examination may be expected to reveal the presence of tubercle bacilli in about 50 per cent of the cases.

The comment to be made on this state of affairs is, that the causes of failure in demonstrating tuberculous bacillaemia as frequently as one should expect lie apparently in the technical difficulties, as is obviously demonstrated by the fact that we frequently fail to demonstrate bacillaemia even in cases in which there is not the slightest doubt of its existence (60 per cent of the cases of acute miliary tuberculosis).

However this situation may stand, we cannot overlook the following facts: The parasitic nature of tuberculous disease was first demonstrated by Villemin (11) by the very fact that the blood of consumptives proved infectious for small animals. The painstaking studies of Liebermeister (12) brought forth an abundance of pathological evidence of dissemination, by the blood-stream, of tubercle bacilli in all forms of tuberculous disease and in many clinically entirely unsuspected conditions, and while the contentions of Loewenstein (13) of the great prevalence of bacillaemia in all forms of chronic pulmonary tuberculosis have been questioned by first-class work in other hands, nevertheless, before Loewenstein as well as since his publications, a considerable number of reliable workers have been able to substantiate Liebermeister's contentions to a considerable degree.

2. PATHOGENESIS OF HAEMATOGENOUS PULMONARY TUBERCULOSIS

There is good reason to believe, as has been emphasized by Loeschcke (14), that one of the principal sources of acute miliary tuberculosis, which is universally recognized to be haematogenous in origin, may be traced to caseating tuberculous lesions, particularly in the lymph nodes

and in connective-tissue structures such as those of the bones. Following the conception of Ranke (7) of generalization in the secondary stage of tuberculosis, it seems most likely that the caseating tracheobronchial lymph nodes are the most frequent source of recurrent dissemination of tubercle bacilli into the blood-stream. In rarer cases of intestinal infection, caseating mesenteric lymph nodes may act in a similar fashion. The easy access of discharges from these lymph nodes into the blood-stream by way of the venous angle makes such blood-stream dissemination easy. In general, available pathological evidence indicates that the opportunities for invasion by tubercle bacilli are so numerous in every phase and form of the infection that it would be surprising indeed if repeated bacillaemia of some degree should be the exception rather than the rule. There exists experimental evidence to indicate that in some cases bacilli invade the lymph-stream from the pulmonary pole of the primary complex almost as soon as implantation took place. The great frequency with which lymph-nodular involvement reaches up to the venous angle has been demonstrated by the notable studies of Ghon, *et al.* (15). Evidence is accumulating that any tuberculous lesion may under favorable conditions secrete tubercle bacilli into the blood-stream. Pascual (16) showed that this was possible from the walls of tuberculous cavities. Liebermeister (17) and Kasper (18) histologically demonstrated beyond doubt the irruption of tubercle bacilli into the blood-vessels from lesions of various sorts. Even so discriminating a pathologist as Loeschcke (14), who recently reëmphasized the points raised by Buhl (19) long before tubercle bacilli were discovered, that in every case of miliary tuberculosis there exists in the body a liquefied caseous focus showing evidence of communication with the blood-stream by haemorrhage, readily concedes the occurrence of subacute and chronic haematogenous tuberculous disseminations due to milder blood-stream irruptions throughout the course of tuberculosis of any form. To-day perhaps the majority of pathologists hold with Huebschmann (20) that the frequency of bacillaemia cannot be estimated and its pathological substrate cannot always be established from pathological evidence, because frequently bacillaemia goes without production of specific changes. Recent pathological studies of Schuermann (21), Pagel (22), Ruedel (23), and others, upon an imposing tuberculous material, established beyond doubt the fact that, in about 35 to 40 per cent of every autopsy material, very characteristic gross and histological evidence of generalized tuberculosis can be demonstrated.

Before discussing in detail the most outstanding pathological features of haematogenous pulmonary tuberculosis, it should be pointed out that pathologists do not yet entirely agree between themselves as to the exact interpretation of these findings. The difficulties of pathological differential diagnosis are stressed particularly by Loeschcke (14), who emphasizes the indistinguishable similarity of some of the features of both haematogenous as well as bronchogenic lesions in the lungs. The difficulty is amply explained by the close anatomical relationship between the bronchus and its artery, as they are situated in the centre of every pulmonic unit. The difficulties are vastly enhanced by the fact that no matter by what route tubercle bacilli reach the pulmonary parenchyma, as the foci progress and ultimately attain the air-spaces, from then on no distinction is possible between the lesions of various pathogeneses.

To the above difficulties there is added the circumstance that, just as bronchogenic phthisis, so pulmonary tuberculosis of haematogenous origin shows evidence of apical predisposition for the incipiency of the phthisical process. It is of extraordinary interest here that haematogenous pulmonary foci have been observed to be capable of absorption in all other parts of the lungs until only the apical or upper-lobe foci remained and progressed to calcification or breaking down. This suggests the possibility of some constitutional, developmental or functional mechanical factor playing a rôle in the predisposition of the upper parts of the lung for the development of phthisical processes, regardless of whether the lesions are derived by the bronchogenic or haematogenous route.

However, in clinching the pathological evidence there comes to our aid the evidence of coexisting extrapulmonary lesions arisen simultaneously with the pulmonary disseminations in such organs of the body which can be reached only by the greater circulation. In the presence of such extrapulmonary tuberculoses the pathological evidence is all the more convincing, since we know that the blood-stream is invaded practically exclusively at the venous side. That infectious blood should pass the lung without leaving a trace in this organ, while at the same time lesions are produced in other organs, is hard to conceive. With Schmincke (24), Redeker (25), Braeuning and Redeker (26), and others it must be argued that haematogenous disseminations restricted exclusively to the lungs are very likely to occur, and indeed do occur, when bacilli are filtered out within the independent vascular bed of the lesser circulation. The likelihood of such a pathogenesis will be all the more striking if we con-

sider that primary tuberculous invasion takes place in the lungs in the overwhelming majority of individuals. Indeed it must be that extrapulmonary disseminations are derived directly from intrathoracic, frequently pulmonary foci. Thus, pulmonary foci may already precede extrapulmonary dissemination, and for the most part are produced simultaneously with them.

The problem of why in some cases tuberculous lesions in the lymph nodes or elsewhere may remain entirely locked up and quiescent during a lifetime, and in others may at intervals discharge tubercle bacilli into the blood-stream, is an unsolved one. It appears largely to be a question of the amount of caseation, the opportunities for communication with blood-vessels, or the accidental occurrences which make up a part of the life of the individual. The writer has been impressed with the fact that there is frequently a connection of some physical strain in the cases showing tendency to recurring disseminations.

The problem of the striking difference between the clinicopathological course following the various haematogenous disseminations is also an unsolved one. In the first place, differences in dosage must be considered. In acute general miliary tuberculosis the assumption is that it is due to irruption of a quantity of tubercle bacilli into the blood-stream, large enough to disseminate itself throughout the entire body. In more chronic cases of haematogenous disseminations one could postulate that the occurrence of periodical discharges of small numbers of tubercle bacilli may be incapable of producing any disease at all, or at other times produce a mild localized reaction with very slight clinical symptoms. Between these two extremes there are types of disseminations standing midway, such as the more or less extensive protracted disseminations seen in children as well as, less frequently, in adults.

In addition to the question of dosage we must raise also the very interesting question of why disseminations "take" in some cases and not in others, and why in the same case they take at some times and not at others. This raises the whole, very debatable question of tissue reaction and immunity. There seems to be little doubt that there are very considerable differences in the susceptibility to a given amount of infection in different individuals, or in the same individual at different times. But whether this is really immunity or not, or whether it is a purely nonspecific constitutional factor, and whether these variations in resistance may vary from one organ to another in the same body at the same time, are questions which are now being widely debated.

Some workers believe that the effect of exogenous bronchial reinfection is not so much the new bronchogenic lesion as it is the effect of reactivating, because of this new infection, dormant lesions of previous haematogenous origin, and that allergy plays an important rôle here. Until more evidence is available, all of these questions must be left open.

3. PATHOLOGICAL FEATURES OF HAEMATOGENOUS PULMONARY TUBERCULOSIS

The pulmonary lesions of acute miliary tuberculosis are easily recognized by their even distribution and uniformity of size and histological features (see figure 1). The miliary tubercle is usually found at postmortem as a more or less fresh lesion embedded in intact lung tissue, frequently associated with hyperinflation (emphysema) of intervening lung parenchyma. The miliary tubercle mostly represents an exudative necrotizing process, but frequently enough it may be a genuine proliferative lesion from the very outset.

In contrast to it, the lesions of protracted disseminated tuberculosis in the lungs are characterized by uneven distribution, although they too are bilateral and symmetrical in arrangement (see figure 2). These lesions are not uniform, polymorphism of size as well as histological features being a characteristic feature. We find, amid genuine miliary-like tubercles, nodular lesions of various sizes, conglomerate tuberculous lesions and larger caseous-nodose processes, which are ready to break or have already broken into the adjacent lymphatics, air-spaces and passages. Hence, protracted dissemination is sooner or later complicated by lesions of lymphogenic as well as bronchogenic spread. The lesions also show marked differences in age by which they can be recognized as belonging to the several successive crops of dissemination.

The lesions of protracted dissemination are associated with marked fibrotic changes in the surrounding lung tissue. In children they are more acute and exudative in character in their earlier stages, and become more caseous and fibrotic in their later stages.

These lung lesions are only one part of the general dissemination which is also characterized by marked caseous involvement of the lymph nodes, especially the tracheobronchial group, exudates into the serous cavities, especially the pleura, and marked disseminated lesions in the spleen and other organs.

The characteristic lesions of chronic haematogenous pulmonary tuberculosis are represented by the exquisitely productive tubercles seeded

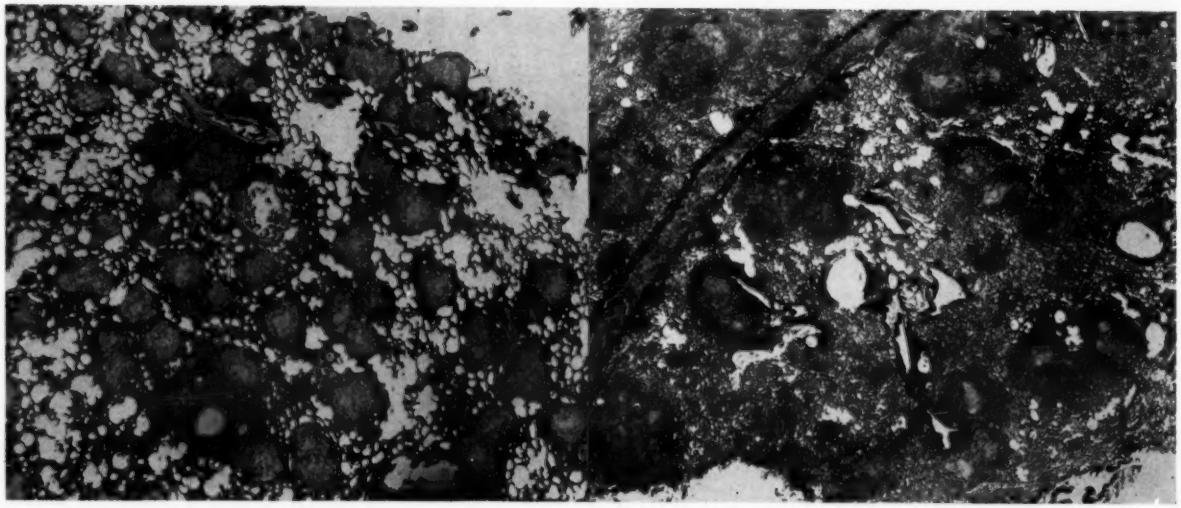


FIG. 1 FIG. 2

FIG. 1. Microscopical appearance of typical miliary tuberculosis in the lungs. Note uniformity in the size and contour of the lesions.

FIG. 2. Microscopical appearance of protracted tuberculous dissemination in the lungs. Note similarity to miliary tuberculosis, but considerable variation in the size and contour of the lesions.

into the walls of lymph- and blood-vessels and into the interlobular and alveolar septa. These are the so-called interstitial tubercles which, due to their productive character, remain covered by unbroken intimal or septal membranes. They do not break into communicating channels and generally show but a mild tendency to coalescence and extension. Instead, they tend to absorption and give rise to much fibrosis. We find residues of most of these lesions especially in the upper lobes in the form of localized or widespread pulmonary fibrosis associated with calcification, giving the features of "burnt-out" haematogenous disseminations, or in that of much thickening of the connective-tissue *interstitium* including the lymph- and blood-vessels, leading to thickening of interlobular and interalveolar septa, going under such names as *reticular lymphangitis* (Schuermann) (21) or *tramite* (Bezançon, *et al.*) (27).

A very characteristic pathological feature of chronic haematogenous pulmonary tuberculosis is the predisposition of the peripheral subpleural zones to receive most of the repeated crops of lesions. It is in these corticopleural zones where coalescence and extension of the lesions are found most frequently. From here, extension is of course frequently toward the pleura by involvement of the pleural layers. Hence, the frequency of pleurisy of haematogenous origin, such as tuberculous pleural effusions in absence of pulmonary phthisis, and the so-called *pleurésie à répétition* (Piéry) (4).

Another characteristic feature of the pulmonary lesions in generalized tuberculosis is the punched-out cavity, as described by Ghon (28), Ranke (29), Schmincke (24), Schuermann (21), Pagel (22), etc. These cavities are characterized by their sharp, thin border embedded in normal or little-changed lung tissue, their ability to enlarge or shrink with a rapidity little short of amazing, and ability to disappear, frequently leaving but a minimal trace. On the other hand, frequently their most conspicuous feature is that they may persist for a long time without giving rise to bronchogenic spread and extension of the process. In contrast to this, the cavity of common pulmonary phthisis is usually embedded in much indurated tissue; usually has a thick, caseous, infiltrated or cirrhotic wall; is slower in its evolution as well as its regression; it rarely disappears without leaving a scar of considerable size; and almost invariably it gives rise to bronchogenic spread and extension of the process.

It is to be emphasized that the above pathological features of chronic haematogenous pulmonary tuberculosis refer to the autopsy aspect of

the process as a whole and its end-result, as manifest at postmortem examination. Any of these features, taken alone or observed severally in a single focus or at any phase of the disease, will not permit valid conclusions as to the nature of the process. Final judgment is thus possible only from consideration of the lesions as a whole, as they appear after death, together with a careful review of their clinical evolution during life.

4. THE CLINICAL FEATURES OF HAEMATOGENOUS PULMONARY TUBERCULOSIS

The practical importance of the conception of haematogenous pulmonary tuberculosis rests upon the possibility of recognizing its forms in practice. This is by no means a simple problem, as we are dealing with a kaleidoscopy of clinical pictures, representing, as has been already repeatedly pointed out, a fluent transition from acute haematogenous dessemination to chronic localized tuberculosis in the lung, recognized under the term of *chronic pulmonary phthisis.*

It is readily conceded that what we recognize as chronic pulmonary phthisis consists for the most part of lesions of bronchogenic origin. Within the range of clinicopathological processes standing between the clear-cut haematogenous miliary dissemination into the lung and the clear-cut chronic isolated bronchogenic phthisis there must exist very numerous pictures representing fluent transitions between the two end-poles. It is to be expected that the clinical processes will bear the stigmata of either haematogenous or bronchogenic origin according to their place in the above mentioned transition, and that recurrent blood-stream disseminations with intervening bronchogenic spreads will tend to produce a great deal of overlapping which makes for further complications that increase the difficulties of delineation of the clinical pictures.

In our own efforts to recognize the clinical pictures of haematogenous pulmonary tuberculosis during life we have found the classifications suggested in the literature to be cumbersome and somewhat confusing. However, inasmuch as many of these terms have come to be rather generally accepted, they cannot be altogether disregarded.

In what follows there will be enumerated some of the more usual of these accepted forms which, after careful study, the writer feels are definitely recognizable clinically. Other forms, which have been described in the literature but which appear to be rather indefinite and certainly debatable, will be merely indicated. The main point emphasized here is, that it is quite feasible to recognize some of these conditions

during life with sufficient certainty to enable one to draw conclusions from such recognition, which are important from the standpoint not only of pathogenesis but of prognosis and treatment.

At the head of the list of the forms of haematogenous pulmonary tuberculosis stands, of course, *acute miliary tuberculosis* of the lung which needs no description, as it is outside the scope of this paper, dealing as it does more with the subacute and chronic forms of haematogenous pulmonary tuberculosis.

Next in line is that clinicopathological process which was first described by Borel (30) and was then introduced by Schuermann (21) under the name of *chronic protracted haematogenous dissemination*, which has of late been studied very carefully at Bellevue Hospital by Grethmann (31). This type of pulmonary disease occupies a position midway between acute miliary and the more localized forms of haematogenous tuberculosis. The lesions of these protracted disseminations, just as in the case of general miliary tuberculosis, involve not only the lungs but also many other organs of the body. They are characterized by extensive caseation of the lymph nodes, particularly of the tracheobronchial group (see figures 3 & 4); by caseating or serous inflammations of the serous membranes, particularly the pleura and peritoneum; and by chronic tuberculous deposits of varying degree and size in the spleen and other organs (see figure 5).

This type of the disease is most common in children, in whom it frequently begins as an acute process, gradually subsiding into a subacute or chronic one. The lesions in the lungs may go on to caseation, but frequently they become stabilized with considerable fibrosis, and often a considerable amount of resolution of the lesions occurs. These acute and subacute pulmonary manifestations in children probably form the basis for the calcified residues noted in the lungs in later life, and are similar in this respect to the behavior of the primary complex itself.

In adults, these protracted disseminations are especially common among the Negroes, Porto Ricans and Mexicans. They regularly run a more chronic course in adults than in children, and, while they are usually slowly progressive until death ensues, not infrequently their course runs for several years. The lesions in the lungs, lymph nodes, serous cavities and other organs, are the same as those already noted in children.

Bard (3), many years ago, described certain definite clinical entities which he recognized as haematogenous forms of pulmonary tuberculosis

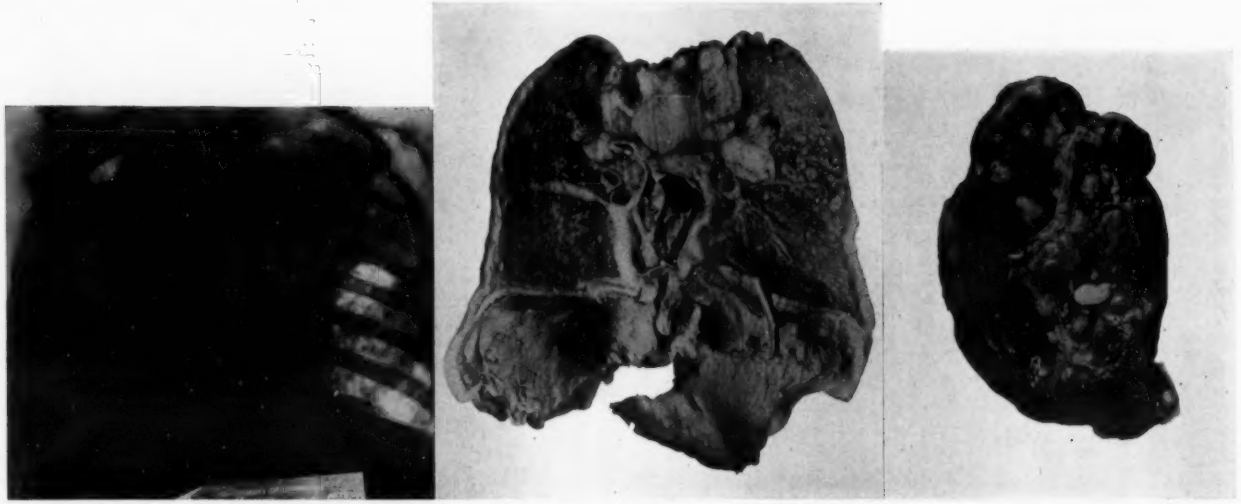


FIG. 3 FIG. 4 FIG. 5

FIG. 3. Roentgenological appearance of a case of protracted dissemination in a child of seven. Note the marked enlargement of the hilum shadows, due to caseating glands, and the disseminated lesions throughout both lung fields. In many cases such lesions may clear and become calcified, appearing in adult life as one or another of the clinical forms described later.

FIG. 4. Same case. Gross pathological appearance of the lesions at autopsy.

FIG. 5. Same case. Showing chronic lesions in the spleen. Note their large size and variation in contours quite different from those of acute miliary tuberculosis.

and which he designated by a very definite terminology which has been largely followed by Neumann (9). The first of these he designated *tuberculosis miliaris discreta*. This form of haematogenous pulmonary tuberculosis is more localized than the preceding forms, but still has some

FIG. 6. Man of 45 years of age. Haematogenous *Tuberculosis miliaris discreta*. Predominantly cortico-pleural arrangement of nodules.

of the characteristics of the more widely disseminated types. This form of the disease is manifest by roentgenological evidence of very fine, disseminated deposits, usually in the upper lobes, very dense and sharply outlined and small in size, representing fibrotic or calcified tubercles (see figure 6).

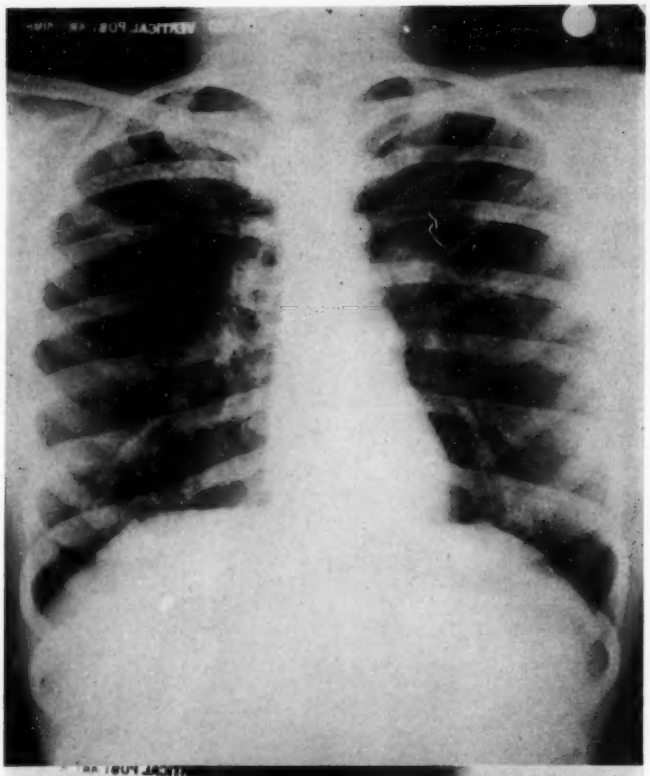


FIG. 7

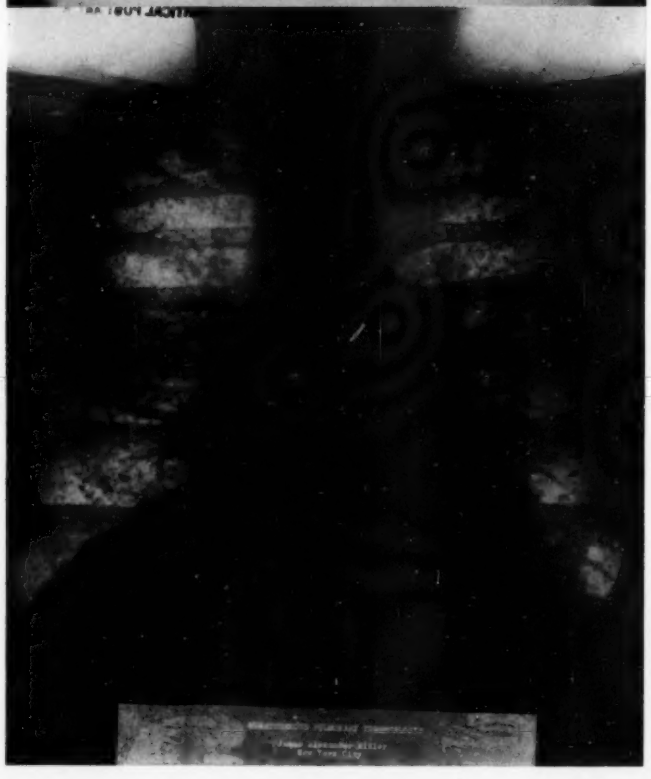


FIG. 8

Many cases in this group present no pulmonary symptoms and the lesions may be discovered accidentally by the X-ray. Frequently, however, there are slight constitutional disturbances not definitely referable to the lung, excepting that slight haemoptyses are frequent, and these disturbances are very apt to be either of digestion or of nutrition.

However, sometimes *tuberculosis miliaris discreta* manifests itself by recurrent crops of fresh tubercles, appearing at varying intervals in portions of both lung-fields (see figure 7). Their appearance may be without symptoms of any kind, or they may be associated with slight fever or other constitutional disturbance. In their course they often gradually diminish in number or may entirely disappear, recurring at intervals of months or even years, or they may become calcified (see figure 8). With them there may be associated evidence of haematogenous disseminations in other organs of the body. This group has been described by the French under the term *granulie* (Delarue) (32), (Rist and Doubrow) (33).

FIG. 7. *Tuberculosis miliaris discreta.* This patient had no cough. Occasional slight rises of temperature associated with roentgenological evidence of exacerbations of the lesions, with intervals of regression.

FIG. 8. *Tuberculosis miliaris discreta,* in which the lesions have become calcified. This patient presented no symptoms.

The next group which Borel described is *tuberculosis fibrosa densa.* This is a clinical entity recognized by characteristic X-ray lesions of sharply localized fibrotic and calcified densities of variable extent in the upper lobes of both lungs. They represent the healed residues of previous haematogenous disseminations (see figures 9, 10 & 11).

Clinically, this group may exhibit no pulmonary or other symptoms and the X-ray lesions are discovered by accident. Other cases are characterized by a state of poor general nutrition, often with prominent nervous symptoms, and usually no (or few) symptoms referable to the lungs. In other cases digestive symptoms of long standing, or cardiovascular or general nervous overirritability, are the outstanding characteristics associated with poor nutrition and notable in the absence of pulmonary symptoms. In other cases the clinical manifestations are small repeated haemoptyses, not associated with fever, and usually without cough or constitutional symptoms.

Still another form he terms *tuberculosis fibrosa diffusa.* This group shows more extensive radiographic lesions in both upper lobes than that

described as fibrosa densa. The roentgenological lesions are characteristically fibrotic, with considerable tendency to calcification. They represent the residues of more advanced lesions from previous haematogenous disseminations (see figures 12 & 13).

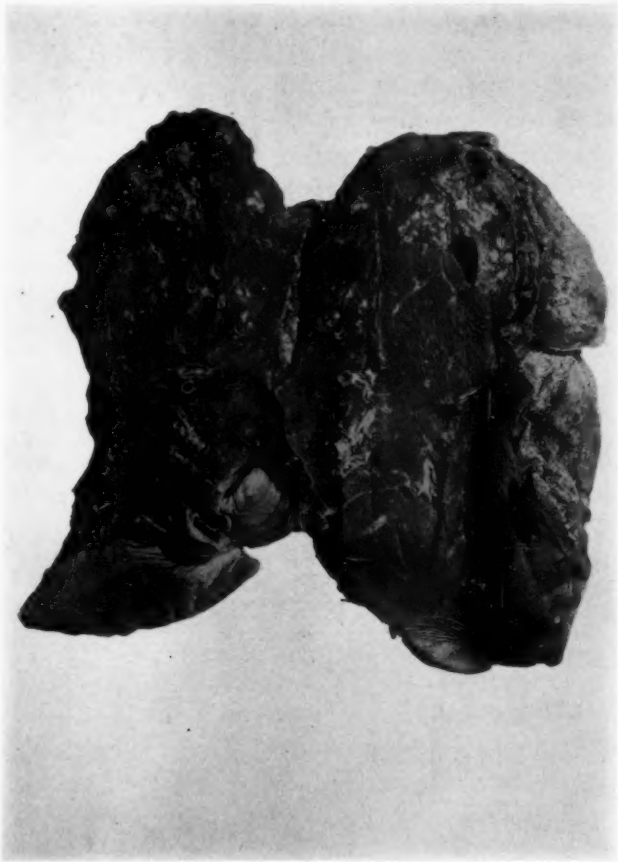


FIG. 9. *Tuberculosis fibrosa densa.* This patient was killed by an accident, with no history of any clinical manifestations of tuberculosis.

Symptomatically, the cases of *tuberculosis fibrosa diffusa* may exhibit any of the various characteristics above described under the various forms of *tuberculosis fibrosa densa.*

A little study easily enables one to pick out these types as described by

Bard (3), even though one may prefer not to use his rather cumbersome terminology.

Another manifestation of tuberculosis which is often probably of haematogenous origin comprises the *pleurisies with effusion* (see figures 14 & 15). Often they are present without definite evidence of intrapulmonary lesions, but more frequently they may be associated with any of the characteristic haematogenous lesions in the lungs and other organs, already described. In the haematogenous cases, pleural exudates are apt to be small, often coming on with comparatively slight constitutional disturbance, and are frequently repeated during the course of years, representing the *pleurésie à répétition* of Piéry (4). As one follows the clinical course of cases with tuberculous pleurisy with effusion, certainly the hypothesis that they may be of haematogenous origin fits into the picture very well.

In the roentgenological study of pulmonary tuberculosis one frequently encounters single or multiple cavities in the lung, with very thin walls, with little or no collateral inflammation, and very slight tendency to bronchogenic spread, which have been termed *punched-out cavities*. Several authors believe that this type of cavity is caused only by infection by the haematogenous route. Frequently such cavities appear as isolated lesions, but more often they are associated with some of the various evidences of intrapulmonary disease already described (see figure 16). The clinical course in such cases is quite different from that of the ordinary bronchogenic cavity, in that the amount of cough and expectoration is slight, the number of bacilli in the sputum is scanty, and there is a marked tendency toward spontaneous healing of these cavities.

It must be recognized that the various types above described are not always sharply defined. Often we find the changes of the various types above described in the same case, and in general the process must be considered as one of a fluent transition of the lesions from the more acute types into those which are more chronic.

Not infrequently, for example, we may see cases with roentgenological evidence of typical *tuberculosis fibrosa densa* or *diffusa* associated with evidences of *tuberculosis miliaris discreta*. The calcified deposits may remain unchanged, while changes represented by the lesions of *miliaris discreta* may clear, or run a chronic course, with exacerbations and remissions, just as in the case of straight-forward *miliaris discreta*. In these cases too, the pulmonary symptoms are frequently very slight, and

FIG. 10

FIG. 11

the outstanding symptom is apt to be dyspnoea on exertion. During exacerbations there may be slight rises of temperature of two or three weeks' duration, and sometimes there are evidences of dissemination in other organs and involvement of the serous cavities such as the pleura and the joints.

In many cases in which any of the above types of pulmonary disease may be roentgenologically evident, the suspicion of tuberculosis is first aroused by the appearance of definite *tuberculosis in some extrapulmonary organ*. This may be the kidneys, bones, joints, spleen, eye, skin, peritoneum, ischiorectal fossa, tubes or ovaries (see figure 17). It has long been recognized that in such cases evidences of tuberculosis in the lungs may be obtained by X-ray examination in a large percentage of cases, and that, usually, there are few or no pulmonary symptoms associated with them. The roentgenological characteristics of these lesions are in every way similar to those already described, and, inasmuch as the haematogenous origin of the proved extrapulmonary tuberculosis is

FIG. 10. Typical roentgenological lesions of *Tuberculosis fibrosa densa*. These undoubtedly represent residues of early haematogenous disseminations, probably in childhood. This patient had no symptoms except inability to gain weight, and disturbances of digestion.

FIG. 11. Another case of *Tuberculosis fibrosa densa*. The only symptom was occasional slight haemoptysis.

indisputable, a similar explanation for the intrapulmonary lesions appears equally certain. In our study of the subject we have been particularly interested in the occasional evidence of such extrapulmonary haematogenous dissemination in the spleen, as shown by roentgenological examination, and, consequently, we are using this method of study routinely when haematogenous tuberculosis of the lung is suspected (see figure 18).

In addition to the above types of cases in which the clinical and roentgenological evidence is definitely in favor of haematogenous dissemination are a number of other types of lesions, held by enthusiastic advocates of the doctrine of haematogenous spread to be of haematogenous origin, which conservatively may better be considered as doubtful, though possible, forms of haematogenous disseminations. Among these forms are:

1: The various forms of diffuse network shadows in the lung fields, interspersed with semilunar X-ray densities. These represent what Schuermann (21) and Pagel (22) have called *reticular lymphangitis*. They claim that these densities represent the remains of previous more marked haematogenous

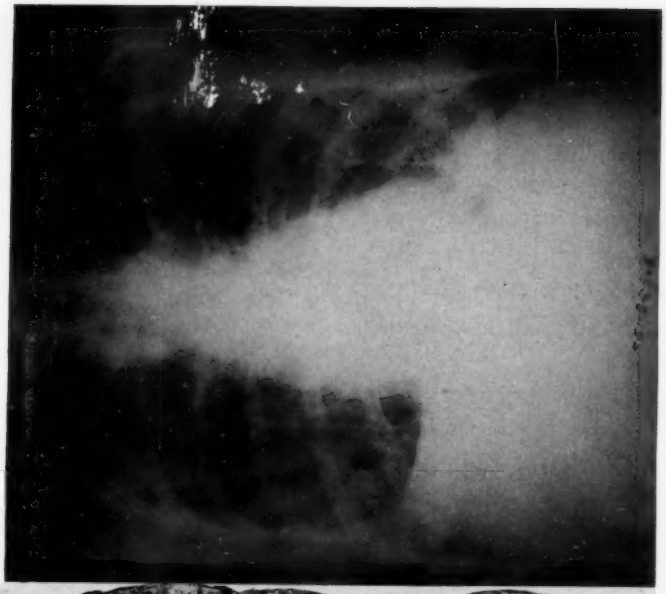


FIG. 13

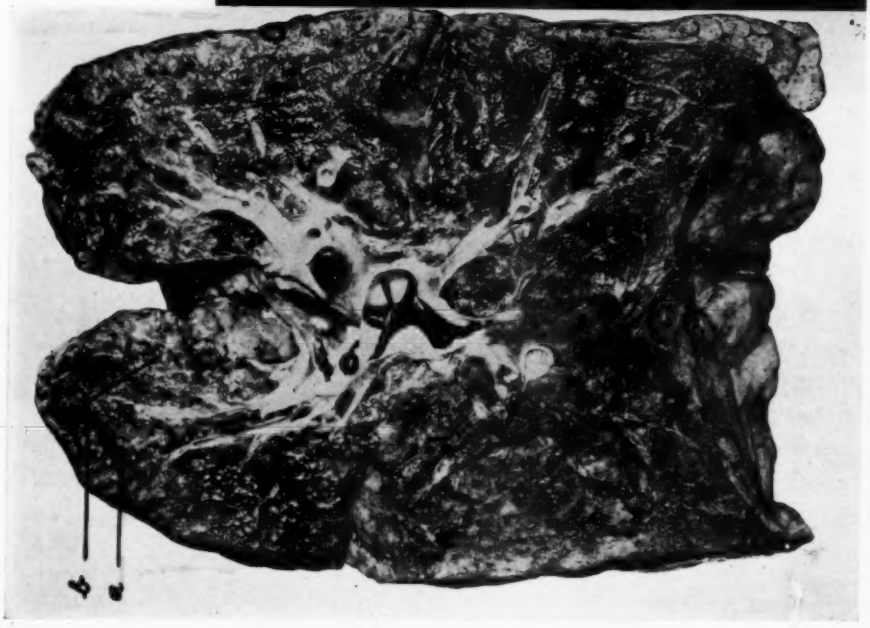


FIG. 12

lesions in which the active infection has been "burned out," leaving a fairly characteristic reticular network, sometimes interspersed with small fibrotic or calcified nodules. The French have described the same type under the term *tramite*, described as a veil-like form of roentgenological densities, from which it receives its name.

2: Many of the advocates of haematogeneous disseminations claim that many of the typical subapical infiltrations, which are usually assumed to be typical of exogenous infection, are due to haematogenous dissemination. Proof of this method of origin of such lesions appears to be dubious.

Inasmuch as much of this clinical evidence leans heavily on roentgenological interpretation, it is only fair to reëmphasize here the limitations of the roentgenological diagnosis of haematogenous pulmonary tuberculosis. We must be aware of the fact revealed so tellingly by a vast experience with lipiodol bronchography, that widespread dissemination of finely dispersed matter by way of the air-passages will exquisitely

FIG. 12. Gross pathological appearance of *Tuberculosis fibrosa diffusa* (b) and small localized areas of *fibrosa densa* (a).

FIG. 13. Roentgenological picture of *Tuberculosis fibrosa diffusa*. This patient had been under observation for eight years, with considerable variation in the roentgenological appearances during that period, and occasional periods of slight fever. There was almost no cough and practically no abnormal physical signs at any time.

reproduce the picture of miliary tuberculosis. This again may be explained by the close anatomical proximity of the vascular tree and the bronchial tree in the lungs. Haemoptysis being so frequent a symptom in the course of pulmonary tuberculosis, the opportunities for producing roentgenographic pictures of miliary-like disseminations are very great. However, this argument should never be used as disposing of the possibilities of such lesions being of haematogenous origin, as indeed the argument may be reversed and it may be pointed out with emphasis that the picture of fine bronchogenic dissemination may, and indeed is, frequently produced by haematogenous dissemination. Thus we have here, as we have in the pathologicoanatomical differentiation, the difficulty of clinical differentiation between haematogenous and bronchogenic forms of pulmonary tuberculosis. All differential diagnosis must therefore never rest upon a single method of examination alone, but must be based on evidence elicited by all available methods of study. The clinical history, the presence of extrapulmonary tuberculous lesions and careful observation of the clinical course, are necessary to enable the

FIG. 14

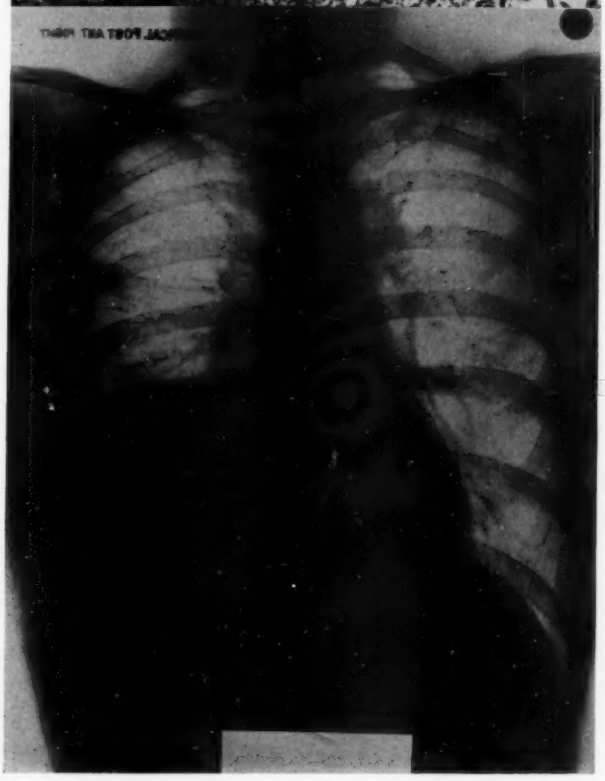


FIG. 15

experienced clinician to settle the question of the pathogenesis with reasonable certainty in a great number of the cases of chronic haematogenous pulmonary tuberculosis.

5. THE CLINICAL COURSE OF HAEMATOGENOUS PULMONARY TUBERCULOSIS

In the clinical recognition of haematogenous pulmonary tuberculosis the careful observation of the clinical course over a prolonged period is of paramount significance for the reason that it shows some characteristics which differ from the course of the typical periodic exacerbations characteristic of common bronchogenic phthisis.

Pathological evidence shows that many of the lesions of haematogenous pulmonary tuberculosis may become absorbed to such an extent as to leave no trace, or leave such residues that can be recognized only by roentgenological methods. From the analogy of what happens in the case of similar haematogenous lesions in the skin and eye, which often entirely disappear, leaving no trace behind, the absorption of haematogenous lesions in the lungs should not surprise us.

FIG. 14. Microscopical pathological appearance of a subpleural haematogenous lesion showing the mechanism of rupture into the pleural cavity in which the exudate already appears.

FIG. 15. Right-sided pleural effusion; slight interlobar pleural thickening. This patient also showed numerous calcified tubercles in the spleen on roentgenological examination. He had been underweight for many years. Responded very promptly to rest treatment, with gain in weight and restoration to normal working capacity.

One of the outstanding characteristics of many of the clinical forms of haematogenous pulmonary tuberculosis, above described, is persistence of the lesions in some parts of the lungs without change over a period of many years. Even when symptoms such as haemoptysis, loss of nutrition, disturbances of digestion, etc., are present, frequently the lesions as shown by the X-ray show no or little change.

In other cases there is a very definite tendency to the recurrence of lesions which may be ascribed to new haematogenous disseminations. This is particularly true in cases of recurrent pleural effusions and in the case of *miliaris discreta* with exacerbations. It is perhaps needless to point out that in cases in which haematogenous disseminations tend to recur (protracted disseminations) the likelihood of an extensive and very acute haematogenous evolution is always present. It is of unusual interest here that the recent studies of Pagel (22) and Ruedel (23), and their analysis of extensive autopsy material at Sommerfeld and Heidel-

berg, show that death from miliary tuberculosis rarely occurs in cases of ordinary phthisis, and that in a very high percentage of such deaths there was present evidence that the phthisical process was derived from lesions of haematogenous origin, that is, represented haematogenous forms of pulmonary phthisis: all of which is in line with the fact that, in

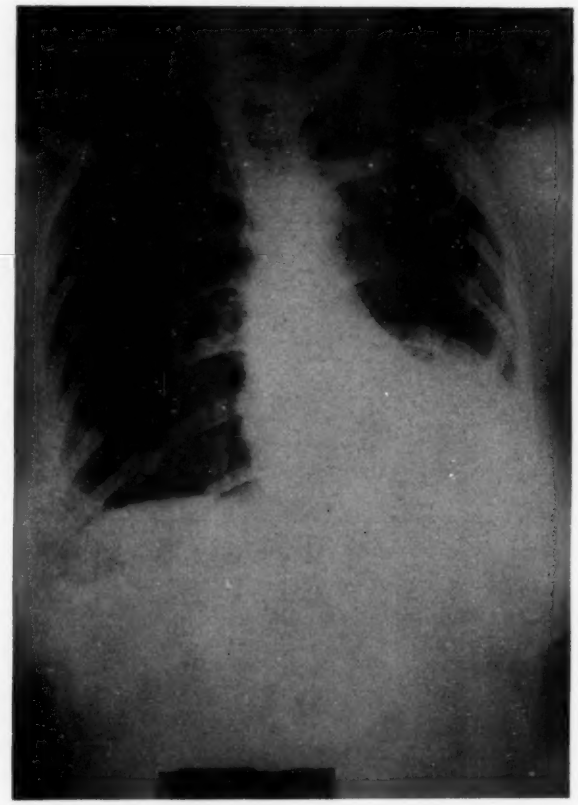


FIG. 16. Roentgenological appearance of a thin-walled punched-out cavity in the left upper lobe, with a pleural effusion at the left base.

cases of haematogenous pulmonary tuberculosis of what might be called an active type, the likelihood of acute dissemination is vastly greater than in the common form of bronchogenic phthisis.

In contrast to this stands the fact, established beyond dispute, that the lesions of chronic haematogenous pulmonary tuberculosis usually show a remarkably sluggish, productive character. This is particularly true of

the lesions beginning in the *interstitium* of the lungs, in the walls of the alveoli and the blood-vessels, which may persist for a period of years and even decades without much progression.

Admitting the probable haematogenous origin of these pulmonary lesions, as has been already pointed out, their evolution frequently develops by bronchogenic spread. As these lesions coalesce, caseate and break down into the alveoli, there is then the same opportunity for bronchogenic spread as in the cases which begin as exogenous bronchogenic infection. Even in these cases, however, it is rather striking that

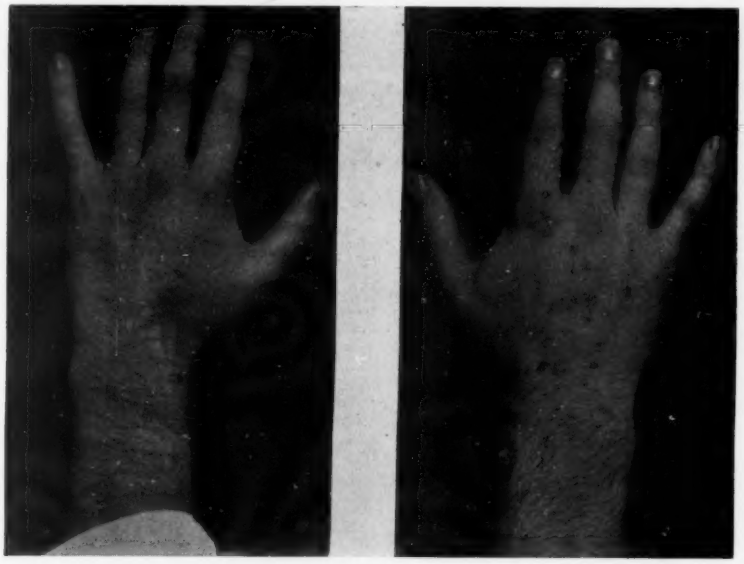


FIG. 17. Typical lesions of papulo-necrotic tuberculides on the hands. This patient had Pott's disease of the spine and typical roentgenological lesions of fibrosa densa in the apices of both lungs.

cases presumed to be haematogenous in origin are apt to be slower in their development and less liable to extensive acute bronchogenic spread than are the cases of infiltrations due to exogenous infection. When, however, involvement of the air-spaces has progressed to a considerable extent, the progression of the disease by means of intracanalicular spread may eventually become the same in the cases of haematogenous origin as in those arisen from bronchogenic infection. It may, therefore, be said that, granted a very considerable proportion of cases of pulmonary tuberculosis arise from endogenous infection through the blood-stream,

the evolution of these cases into ordinary phthisis is by bronchogenic and other intracanalicular spread, just as in the cases of exogenous infection. Any effort to accurately determine which of such advanced

FIG. 18. Roentgenological evidence of calcified tubercles in the spleen. This patient also had calcified lesions in the apices of both lungs. Complained of chronic indigestion and loss of weight. Intestinal X-ray studies revealed the condition in the spleen, and this led to correct diagnosis.

cases were exogenous or endogenous in origin would appear to be futile in the majority of the cases.

It is to be emphasized that, while a very large number of cases of presumed haematogenous pulmonary tuberculosis are characterized by a

very benign and chronic course of very slight clinical significance, on the other hand the transition of such cases over into ordinary bronchogenic phthisis is common, and when this occurs it is impossible of accurate differentiation from ordinary bronchogenic phthisis with all of its uncertainties of prognosis.

6. THE GENERAL AND PRACTICAL SIGNIFICANCE OF THE CONCEPT OF HAEMATOGENOUS PULMONARY TUBERCULOSIS

It is of course obvious that the question raised as to whether adult pulmonary tuberculosis is frequently due to an endogenous infection from an earlier childhood disease, or whether it is almost invariably due to exogenous adult reinfection, has its very important bearing not only upon the pathogenesis of tuberculosis but also upon its epidemiology. It also may have an important bearing on treatment.

The recent evidence in favor of an important percentage of cases of adult pulmonary tuberculosis being due to endogenous infection through the blood-stream is too strong to be lightly cast aside. In our studies over the past three years, since we have been particularly interested in this phase of the tuberculosis problem, we should estimate that somewhere between 20 to 30 per cent of all cases of pulmonary tuberculosis may be reasonably ascribed to such haematogenous dissemination. Many authors place the proportion much higher, even as high as 50 or 60 per cent. This of course revives the notions held so many years ago by von Behring (34); it emphasizes the particular importance of childhood infection and the necessity of careful and prolonged treatment of cases of childhood disease. It also emphasizes the importance of intercurrent factors of disease and strains in life as the exciting cause of the development of clinical adult pulmonary tuberculosis.

This hypothesis, on the other hand, diminishes to just this degree the emphasis which has in recent years in this country been placed upon the dangers of adult reinfection. That the truth in the matter lies somewhere between the extremes held by the enthusiastic supporters of these two schools is probably reasonable to believe.

In the matter of treatment, the recognition of this group of cases leads to a very considerable and important modification of our ideas. I am convinced that many of these cases need no treatment at all, and that we are wasting many months and years of active life and sanatorium and hospital beds needed for other cases, in the unnecessary treatment of many of these cases. On the other hand, the response to rest and the

protective influence of physical and other strains in cases in which these conditions have been recognized afford us a basis for optimism and hopefulness in the comparative ease by which these cases may be restored to normal health and kept there.

The benign nature of these haematogenous pulmonary lesions in many of their manifestations offers the opportunity for obtaining excellent results by rest treatment, and the variations in the character of the lesions suggested by our ideas of varying immunological reactions suggest the possibility that in this type of cases some form of specific therapy might be considered particularly hopeful.

If there is any basis for the idea that not only the amount of dosage is important but also the specific reaction of the tissue in which the comparatively small number of tubercle bacilli lies, then it would appear that efforts to change artificially the reaction of the tissues to meet such comparatively small, though repeated, dosages of infection, might be fruitful in results.

Certain of these lesions, particularly those associated with the characteristic punched-out cavities, have apparently very different significance from the ordinary fibrocaseating phthisis. Not only is the prognosis better and the course more benign, but many of these cavities heal spontaneously, and because of their thin walls may collapse entirely. Probably these lesions represent some of those which we previously described under the name of *annular shadows*, and possibly also the spectacular results of mechanical therapeutics, such as phrenicectomy and artificial pneumothorax, may be due to their benign character and tendency toward spontaneous disappearance. It would appear important, when lesions appear to be of this character, to watch the patient over a definite period of time with strict rest before instituting radical or mechanical methods of treatment, as spontaneous improvement so often occurs.

In general, a study of this whole interesting field of the possibilities of pathological, epidemiological and clinical implications of the hypothesis of haematogenous pulmonary tuberculosis would appear indicated, particularly in this country, where up to the present time our thinking has been largely dominated by the school of thought which explains adult pulmonary tuberculosis largely in terms of adult exogenous reinfection.

I wish to gratefully acknowledge my indebtedness to Dr. Wolfgang Grethmann for material assistance in the presentation of the pathological phases of this subject, and to Dr. Edith Lincoln in charge of the Lung Division of the Children's Service, Bellevue Hospital, under

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A FLUID-VALVE IN PYOPNEUMOTHORAX

HALLIDAY SUTHERLAND[1]

Spontaneous rupture of the collapsed lung is a not infrequent accident in the treatment of pulmonary tuberculosis by artificial pneumothorax. The case here recorded was also complicated by a pleural effusion which made a fluid-valve. On inspiration, when the effusion fell below the level of the rupture, air was drawn from the ruptured lung into the pleural cavity. In expiration, when the effusion rose beyond the level of the rupture, this aspirated air was trapped above the fluid. Thus air-pressure in the upper part of the pleural cavity was increased, and displaced the mediastinum.

CASE HISTORY

The patient, unmarried, aged 27, had no family history of tuberculosis. During the summer of 1926 in New York she had cough, with loss of appetite and weight. In November, 1926, at Geneva, tubercle of the right lung was diagnosed, and tubercle bacilli were found in the sputum. From Christmas, 1926, to April, 1928, she stayed in a sanatorium, where she was treated with tuberculin, calcium, and sanocrysin. She left uncured, and consulted me in July, 1928.

Clinical Signs

A slender-built brunette, she weighed 108 lbs. (7 st., 10 lbs.) for a height of 5 ft., 7 in. She had paroxysmal cough with 2 oz. of sputum a day. Tubercle bacilli were present. The patient's appetite and digestion were not impaired, and the menses were normal. She had continuous fever (100° to 102°F.) with night-sweats. Pulse 96–120. The right lung, except in the apical region, showed signs of extensive disease: marked dulness, bronchial breathing, râles and crepitations, increased vocal resonance and fremitus, and below the second rib anteriorly were signs of a cavity. Apart from slight dulness over the upper lobe the left lung seemed clear. These clinical signs were confirmed by a radiogram which showed extensive mottling and a cavity on the right side, with slight mottling and peribronchial infiltration around the root of the left lung.

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Artificial Pneumothorax

On July 14th I began to collapse the right lung, and in five days 1550 cc. of air had entered the pleural cavity. A radiogram of the completed pneumothorax showed that the only adhesions were posterior and in relation to the 5th, 6th and 7th ribs in the midscapular line, but this radiogram also showed that mottling was more marked around the left hilum. The continuous fever gave place to a mild intermittent pyrexia (97.4° to 99.2°F.), and the sputum was reduced from 2 to 1½ oz. The patient was under constant medical and nursing supervision for 2½ months, having weekly and then fortnightly refills. At the end of this time the temperature was normal, and she was up all day. The sputum was reduced to ½ oz. a day.

During the last three months of 1928 the patient stayed with friends in London, and came to see me for weekly injections of tuberculin and fortnightly refills. She felt well, and refused to regard herself as an invalid. She was too busy to take her temperature regularly, and when it was obvious that the temperature chart was being faked I stopped the tuberculin. The discipline of a sanatorium would have helped her, but she declined to go.

Rupture of the Lung

At the beginning of February, 1929, after an interval of a month, she came to see me. The sputum had increased to 2 oz. and she had continuous fever (99° to 100°F.). Pulse 96–120. She then entered a nursing-home, and on February 7th I gave a refill of 900 cc. of air, leaving a positive pressure of 2 in. water. On the following day there was a febrile reaction. It would have been better to have left a zero pressure, but I do not associate the positive pressure with the accident, because on the 2nd and 3rd days the temperature was normal, and there was no discomfort in the chest. On the fourth day the temperature rose to 101.4°F. It remained at this level on the fifth day, when she developed nasal catarrh with blood-stained discharge, and had one attack of vomiting. I treated this as influenza. On the morning of the sixth day she felt better, but at 4 P.M. the right lung ruptured, and that night the temperature rose to 104.2°F.

Symptoms and Signs

The patient had no premonition of the rupture. Nor was there pain. She had been sitting up in bed, and suddenly felt "something give way" in her chest. In a moment she had the sensations of suffocation and impending death. I saw her within an hour of the onset,—respirations 36, pulse 120 and temperature 103.4°F. The main symptoms were those of shock. Her face was pale and anxious, the lips slightly cyanosed, and the surface of the body was cold and moist despite the fever. The immediate treatment was a hypodermic of morphia ⅓ gr., hot-water bottles, and oxygen. On the right side the

percussion note was tympanitic, but of lower pitch than it had been over the artificial pneumothorax. There was also high-pitched amphoric breathing, whispering pectoriloquy, and the ringing-bell sound.

When traumatic pneumothorax occurs in a lung hitherto uncollapsed, shock is due to the sudden cessation of breathing in one lung, and to stasis of the pulmonary circulation on one side, which causes venous engorgement of the right ventricle. Shock is most severe when a large rupture leads to rapid collapse of a lung not bound by pleural adhesions, and when the other lung has not developed its power of compensatory respiration. Shock is also severe when the rupture is in the less-affected lung, because the more-diseased lung cannot undertake the respiratory work of its neighbor. For the same reasons shock is less severe when a small rupture causes a gradual escape of air into the pleural cavity, or when a sudden collapse of the lung is prevented by adhesions, or when in extensive chronic disease the other lung has already established compensatory respiration.

Thus the immediate consequences of spontaneous rupture in a lung collapsed by artificial pneumothorax should be less serious than in traumatic rupture of an uncollapsed lung. The latter occurred in 17 out of 263 consecutive fatal cases of pulmonary tuberculosis tabulated by Horton Smith Hartley (1). Half the cases die within the first week, and only 10 per cent of all cases eventually recover.

In this case the pulse-rate, strength of the heart, and the fact of the rupture having occurred in a lung already collapsed, were in favor of the patient surviving the immediate danger. That night Lord Horder saw the case in consultation, and again three days later when signs of hydropneumothorax had appeared,—metallic tinkling and the succussion splash. The almost inevitable occurrence of a pyopneumothorax was considered, and it was decided not to interfere unless symptoms of intrapleural pressure were apparent, and then to aspirate either air or fluid according to circumstances.

The Fluid-Valve

The level of the fluid, as mapped out by percussion, rose gradually, until on March 5th, twenty days after the rupture, it was above the level of the 3rd rib at the sternum. Amphoric breathing had disappeared, and there were signs of pressure,—"a bricky feeling in the chest," mediastinal fluttering, and displacement of the heart toward the left. A puncture in the 4th intercostal space in the anterior axillary line and above the fluid gave a positive air-pressure of 6 in. water. I withdrew 300 cc. of air, leaving a negative pressure of −1 inch, and this relieved the symptoms.

Three days later (March 8) pressure symptoms returned, and above the fluid the air-pressure was +4 in. water. Again 300 cc. of air were aspirated, and symptoms relieved. The increase of air-pressure within three days of its

removal and the absence of any apparent increase in the amount of fluid suggested a valve. This was confirmed by a radiogram on the same day.

Hydrostatics of the Fluid-Valve

The radiogram shows that the lung collapse is greater than under the artificial pneumothorax, and that on inspiration the fluid is below the open valve.

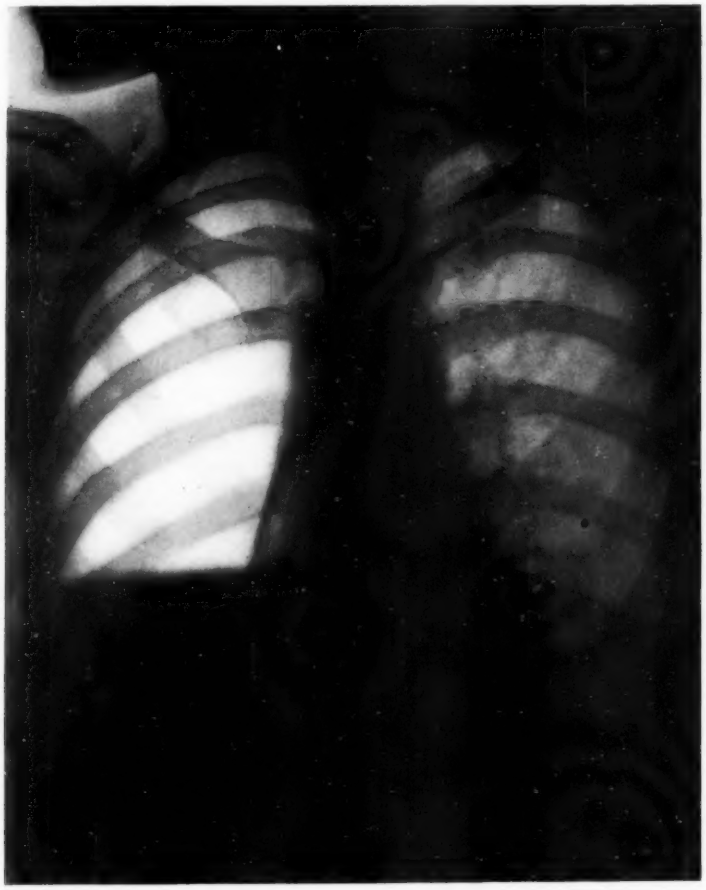

FIG. 1. THE FLUID-VALVE

On inspiration the surface of the pus is just below the rupture with its flap of overhanging pleura, now open. Level of fluid $3\frac{3}{4}$ inches from the claviculosternal joint. (March 8, 1929.)

The flap of the valve is the pleura hanging over the ruptured cavity. On expiration the effusion rose above the rupture, and the pressure of the fluid kept the valve closed. That explained why no pleural fluid had entered the lung,

and why no pus had been expectorated. On inspiration the level of the fluid fell, and air was drawn into the pleural cavity. On expiration the level of the fluid rose, closed the valve, and thus trapped the air above the effusion. For that reason I have named this condition a "fluid-valve." On inspiration the surface of the fluid meets the lung above the third rib $1\frac{3}{4}$ in. from the midsternal line, and $3\frac{3}{4}$ inches below the lowest point of the right claviculosternal joint. I chose this as a fixed point from which subsequent levels of the fluid could be measured. This radiogram also showed an increase of disease around the left hilum.

Aspiration of the Effusion

On the following day (March 9) I withdrew 9 oz. of fluid through the 5th right intercostal space, in the anterior axillary line. After removal of the fluid amphoric breathing was again heard, which proved that without the pressure of the fluid the rupture did not function as a valve. The fluid drawn off was pus with tubercle bacilli present. The pus cells were very degenerated, and cultures of the pus showed streptococci and a coliform bacillus. The calcium content of the fluid was 13.4 mgm. per 100 cc. On March 12th amphoric breathing was still present and the interpleural air pressure was zero to -2 inches, showing that the valve was open. The temperature had settled down, and was now only a few points above normal. Pressure symptoms returned on April 12th, and 7 oz. pus were withdrawn.

A radiogram on April 17th showed expansion of the right lung below the fluid, the level of which was thus raised by $\frac{1}{4}$ inch. On inspiration the surface of the fluid meets the lung below the third rib 3 in. from the midsternal line, and is $3\frac{1}{2}$ in. below the lowest point of the right claviculosternal joint. The rupture in the right lung has closed, but there is more disease around the left hilum. Air-pressure in the right pleural cavity was -2 in. to $+1$ in. (April 18, 1929.)

A radiogram on May 2, 1929, showed on inspiration the surface of the fluid meeting the lung above the 3rd rib, $2\frac{3}{4}$ in. from the midsternal line, and $2\frac{3}{4}$ in. below the lowest point of the right sternoclavicular joint. The level of the fluid had thus risen $\frac{3}{4}$ inch.

The radiograms showed progressive disease in the left lung, and on May 7, 1929, symptoms and signs of dry pleurisy appeared alongside the cardiac reflection of the pleura. These facts, together with physical and X-ray signs of a cavity forming in the left lung, led me to decide to aspirate the pus even in the absence of pressure symptoms. The fluid firstly was hindering restoration of breathing in the right lung, and therefore putting an unnecessary strain on the left lung, where the disease was now active. Second, the effect on the right lung was an obstacle to the induction of pneumothorax on the left side if that should become imperative.

The pus was aspirated through the 4th intercostal space in the midaxillary line as follows: 8 oz., May 10; 1 oz., May 19; 3 oz., June 2; and 4½ oz., June 14, 1929.

This pus contained tubercle bacilli, and films showed masses of microörganisms. (The patient's temperature was now normal.) Streptococci were no longer present, but on cultures coliform bacilli, diphtheroid bacilli, and *Staphylococcus aureus* were grown. The calcium content of the filtrate was 9.78 mgm. per 100 cc. (May 10, 1929.)

A radiogram on June 15, 1929, showed further expansion of the lung below the fluid. On inspiration the surface of the fluid meets the lung above the 3rd rib, 3 in. from the midsternal line, and is 2½ in. below the lowest point of the right claviculosternal joint. The level of the fluid had therefore risen 1 inch since April 17, 1929. Extensive disease is shown in the left lung.

The remaining pus was then aspirated, 4 oz. on June 22 and 2 oz. on July 1, 1929. A radiogram (July 2, 1929) shows partial pneumothorax after complete aspiration of the pus.

Therapeutic Measures

The main drug treatment was calcium chloride in doses from 10 up to 120 gr. four times a day, two hours after food; for example, 1 oz. a day. With a view to raising the level of blood-calcium 8 subcutaneous injections of parathyroid hormone (Lilly) were given over a period of two months in doses of from 2 to 16 units. On the day following an injection of 5 units the blood-calcium was 8.93 mgm. per 100 cc. Two days after a dose of 14 units, blood-calcium was 8.89 mgm. Before the last injection of 16 units the blood content was 9.18 mgm. and on the following day 8.69 mgm. At no time did the blood-calcium reach the normal of 10 to 11 mgm. per 100 cc.

The pus on March 9, 1929, had a calcium-content of 13.4 mgm. Two months later, after the course of parathyroid hormone, the calcium-content was 9.78 mgm. per 100 cc. For three months a portion of yeast, the size of a walnut, was given daily.

Subsequent History

July, 19, 1929, I sent the patient to a sanatorium and have had the following reports: For two years it was necessary to wash out the pleural cavity above the right lung from its posterior aspect. On September 16, 1930, a left artificial pneumothorax was induced, which up to now has been maintained. The patient's larynx also became involved, and was twice cauterized, but she is now able to use her voice. She has had two courses of sanocrysin. From the last report of February 25, 1932, three years after the rupture: "The patient is up and about, though not capable of taking any appreciable walks, for the greater part of the day—the right lung is now a fairly useful one though small, and

there is still at the posterior aspect at the top of it a sac with thickened walls and containing a little fluid. The condition of this side is stationary. . . . She has still some cough and expectoration and tubercle bacilli are nearly always present, though only in small numbers. Her weight is stationary at about 8 st. 1 lb. [113 lbs.] for the last year. . . . About a year ago she dropped ½ st. [7 lbs.] in weight."

REFERENCE

(1) HARTLEY, H. S.: Brompton Hospital Reports, 1903.

ANATOMICAL CHANGES IN THE DIAPHRAGM FOLLOWING PHRENICECTOMY

A Report of 11 Necropsies[1]

W. STUART STANBURY

Phrenicectomy in the surgical treatment of chronic pulmonary disease has enjoyed considerable popularity during the past five years. In this interval over 10,000 cases have been reported in the literature. Widely divergent views have been expressed as to its clinical value, both as a single therapeutic measure and as a supplementary operation to extrapleural thoracoplasty. It is surprising that, with such a large series, so few postmortem studies are available to give us a better understanding of the anatomical end results of this form of therapy.

Meisezahl (1) in 1925 reported a necropsy on a patient who had received therapeutic phrenicectomy fifteen months before death. His is the only study on human postmortem material that has been published. Meisezahl described the paralyzed half of the diaphragm as a thin, whitish, translucent membrane contrasting markedly with the thick red musculature of the unparalyzed side. Histologically he found only a few atrophic muscle fibres. He examined with particular care the digitation to the 12th rib, and found the atrophy to be as pronounced here as in other portions of the paralyzed leaf.

A few reports of diaphragmatic atrophy, apparently associated with accidental involvement of the phrenic nerve, are to be found in the literature. Glaser (2) reported marked atrophy of the left side of the diaphragm in a man dying from carcinoma at the base of the tongue. Doering (3) described a left-sided atrophy associated with cardiac insufficiency. Tennant (4) noted a partial atrophy involving the posterior two-thirds of the left diaphragm in a case of tertiary syphilis. He was, however, unable to demonstrate any lesion of the phrenic nerve. Fergusson (5) reported atrophy of the diaphragm associated with progressive muscular atrophy.

During the past few years a number of experimental studies have

[1] From the Pathological Laboratories, Mountain Sanatorium, Hamilton, Ontario, Canada.

appeared, describing the effects of phrenic neurectomy in dogs and the type and distribution of the supervening atrophic changes in the diaphragm. Schlaepfer (6) (7), Lemon (8) (9), and Andrei (10) have described a uniform atrophy of one-half of the diaphragm following the evulsion of the corresponding phrenic nerve. The line of demarcation between the normal and paralyzed halves of the diaphragm was sharply defined at the midline in all animals used by both Schlaepfer and Lemon. Lemon and Andrei, by examining their dogs postmortem at varying intervals from two days to five months after operation, have been able to observe the progressive changes in the diaphragmatic musculature following section of the phrenic nerve. While, in essentials, the findings of these investigators are in agreement, there is no unanimity as to the exact nature of the degenerative processes.

In the autopsy service of the Mountain Sanatorium we have had the opportunity of studying 11 tuberculosis cases on which some type of phrenic-nerve section had been performed. In ten of these cases the phrenic nerve was evulsed by the method of Felix. In one (case 5) no definite record is available, and it is impossible to say whether evulsion or simple section was done. Nine of the operations were on the right side and two on the left. In 8 cases phrenicectomy was done as a single procedure, and in three it was supplementary to extrapleural thoracoplasty. In all, the supervening paralysis of the diaphragm had been established clinically. The intervals between phrenicectomy and death were as follows: three weeks, four months, fourteen months, seventeen months, nineteen months, twenty months, two years, four years, four and one-half years, and six years. The series is made up of 6 males and 5 females. Age varied from twenty to fifty-seven years with an average for the group of 39 years. Death was due to tuberculous enteritis in one case, bronchopleural fistula and amyloid disease in one, perforated gastric ulcer with generalized peritonitis in one, secondary haemorrhage following extrapleural pneumolysis in one, pyelitis and chronic nephritis in one, acute dilatation of the heart in one and gastroduodenal ileus in four. The high incidence of gastroduodenal ileus in this small series is noteworthy and will be discussed later.

GROSS APPEARANCE OF THE PARALYZED DIAPHRAGM

The sudden death of one of our patients (case 10) within three weeks of phrenicectomy gave us an opportunity to study the early changes in the paralyzed musculature. On viewing the diaphragm from the abdominal

surface, the paralyzed right half rose in an even concave dome to the level of the midportion of the 4th rib. The left was in the 5th interspace. The paralyzed half was of a pale pink color, contrasting with the beefy

FIG. 1

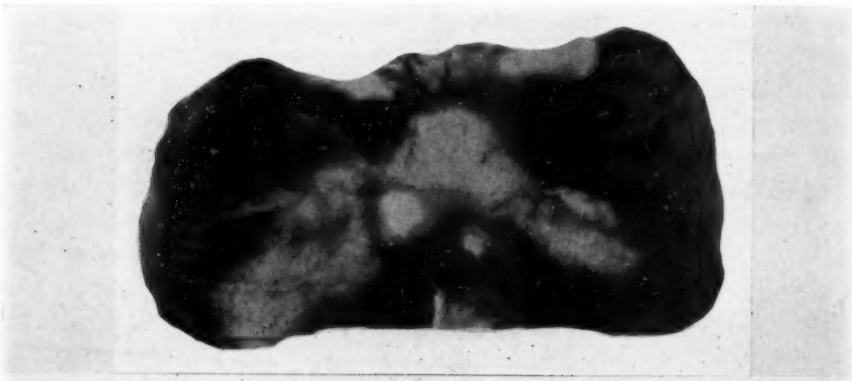

FIG. 2

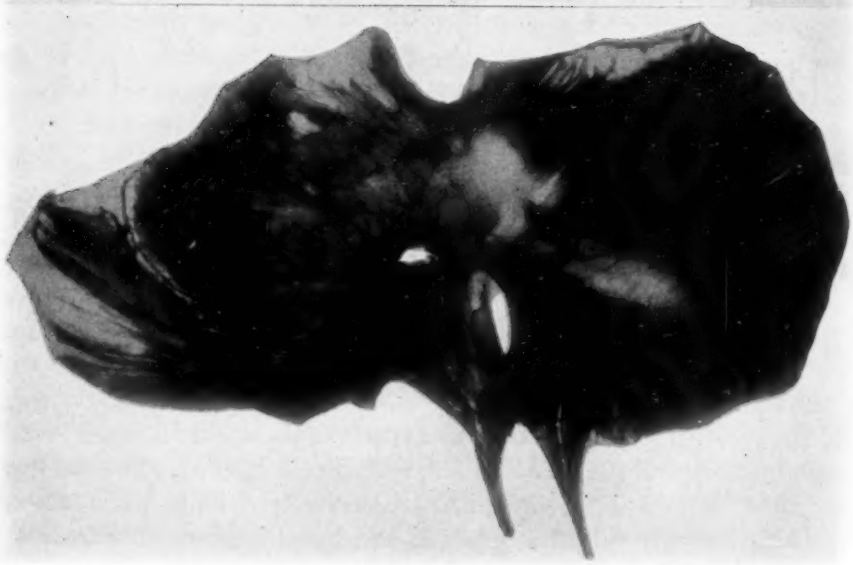

FIG. 1 (Case 10). Diaphragm 3 weeks after right phrenicectomy. Transmitted light
FIG. 2 (Case 6). Diaphragm 4 months after right phrenicectomy. Transmitted light

red musculature of the opposite side. Anteriorly, it was difficult to make out the line of junction of muscle with central tendon. There was very definite thinning of the musculature of the paralyzed side. This was appreciable both at the periphery and along the margin of the oesophag-

al hiatus. The paralyzed leaf averaged 3.5 mm. in thickness as compared with 5 mm. for the normal musculature of the opposite side.

FIG. 3

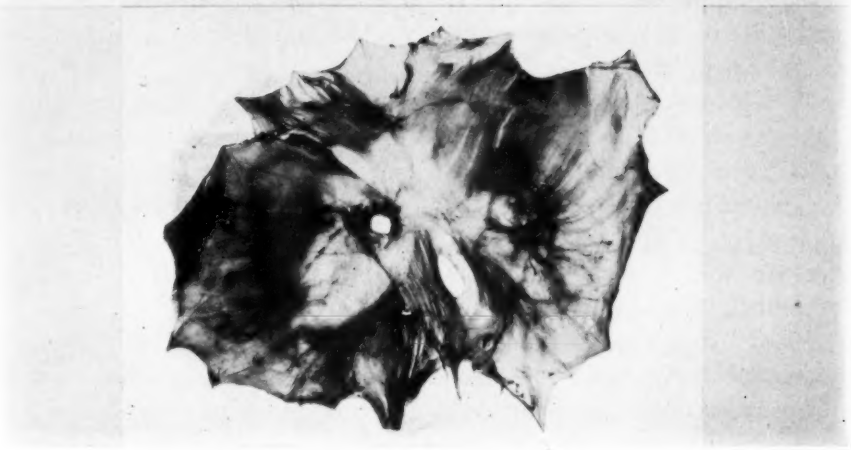

FIG. 4

FIG. 3 (Case 8). Diaphragm 17 months after right phrenicectomy. Transmitted light
FIG. 4 (Case 5). Diaphragm 4½ years after left phrenicectomy (?). Transmitted light
Note some remnants of muscle in the sternocostal portion of the left leaf

Nine of the diaphragms, in which the duration of paralysis was much longer, all presented a similar gross appearance. The paralyzed half of

the diaphragm appeared as a pale, translucent, parchment-like membrane rising into the thorax. Its pallor contrasted in a striking way with the dark red muscle of the unparalyzed side. The line of separation between the paralyzed and nonparalyzed leaves was sharply drawn at the midline anteriorly from the sternum to the oesophageal hiatus. The margin of the oesophageal hiatus toward the paralyzed side was definitely thinner in all cases, but in four of the nine diaphragms under discussion a few poorly defined muscle fibres could be made out in this area by transmitted light. In the remaining five no muscle could be seen on gross examination. The crus of the diaphragm on the paralyzed side was greatly reduced in size and apparently atrophic to its vertebral attachment. From the midline to the extreme periphery the atrophy of the diaphragm appeared to be universal. Through this thin translucent membrane the underlying organs could be seen distinctly. When corresponding areas of the two sides are compared, the paralyzed portion is found to be from one-quarter to one-third the thickness of that on the opposite side.

One diaphragm of the series (case 5) did not conform to the above description. By transmitted light a few poorly defined, thin muscle fibres could be seen in the sternocostal region of the paralyzed left dome, as well as along the outer margin of the oesophageal hiatus. With the exception of these areas the atrophy was uniform and complete to the extreme periphery.

In all cases of the series, the dome of the diaphragm on the paralyzed side was elevated into the thorax to a varying degree. A minimal rise to the level of the midportion of the fourth rib was noted in case 10, and a maximum rise to the level of the upper border of the third rib in cases 4, 5 and 9. The maximum rise of the dome after right and left phrenicectomy was the same in this series, although the average rise attained was much greater after section of the left phrenic nerve.

Viewed from the abdominal surface, the paralyzed half of diaphragm presented an even concave surface except in cases 1 and 3. In these cases the rounded dome was distorted by an umbilication at the posterolateral margin of the right leaf of the central tendon. A pouch-like invagination of tendon and neighboring atrophic muscle, rising further into the thorax, incarcerated a large, rounded, knob-like malformation of the right lobe of the liver. The diaphragmatic leaf was gathered around the base of this protuberance to form a firm constricting ring.

HISTOLOGICAL DESCRIPTION OF THE PARALYZED DIAPHRAGM

The histological study of the diaphragms of this series was undertaken with some care. Not only did we wish to examine the nature of the muscular atrophy, but also its extent and distribution. In view of the controversy as to the exact motor innervation of diaphragm, this seemed an excellent opportunity to investigate the question with human postmortem material.

The diaphragms were removed intact with the lungs, heart and oesophagus. The costal digitations and the vertebral attachments of the crura were dissected out carefully. The organs were hardened in Kaiserling I for at least 24 hours. The diaphragms were then dissected from the lungs and placed upon a wooden frame. They then were photographed by transmitted light. With the organ lightly stretched on a rectangular frame, blocks of tissue were taken from the midline to include equal portions of right and left halves of the diaphragm, from the sternal attachment to the vertebral insertions of the crura. An average of seven blocks was taken from the midline, including the sternal attachment and regions just anterior and posterior to the oesophageal hiatus, and both lateral margins of the orifice. Further blocks were taken from the peripheral attachments, including the digitations to the twelfth rib, the junctions of the musculature with the central tendons, the lumbocostal arches and the crura of the diaphragm, to include a portion of their tendinous attachment. In every case control areas were taken from corresponding points of the unparalyzed side. In addition to our study of this series, we examined eight apparently normal diaphragms. These were obtained from routine postmortems at the Mountain Sanatorium, and were therefore questionable controls. All of this control series died of tuberculosis. The average age for the group was 32 years.

All tissue was embedded in paraffin. Blocks from the same areas were also embedded in gelatin, and cut on the freezing microtome. Sections were stained routinely with haematoxylin and eosin, Mallory's fibrous-connective-tissue stain, Verhoeff's elastic-tissue stain, and Scharlach-R with alum-carmine. A number of sections were stained with Van Gieson's picro-fuchsin as well.

As early as the third week after phrenicectomy, definite histological changes can be made out in the musculature of the paralyzed diaphragm. The nuclei appear to be increased in number. The muscle fibres, on an average, are definitely smaller than those noted in corresponding areas of

FIG. 5

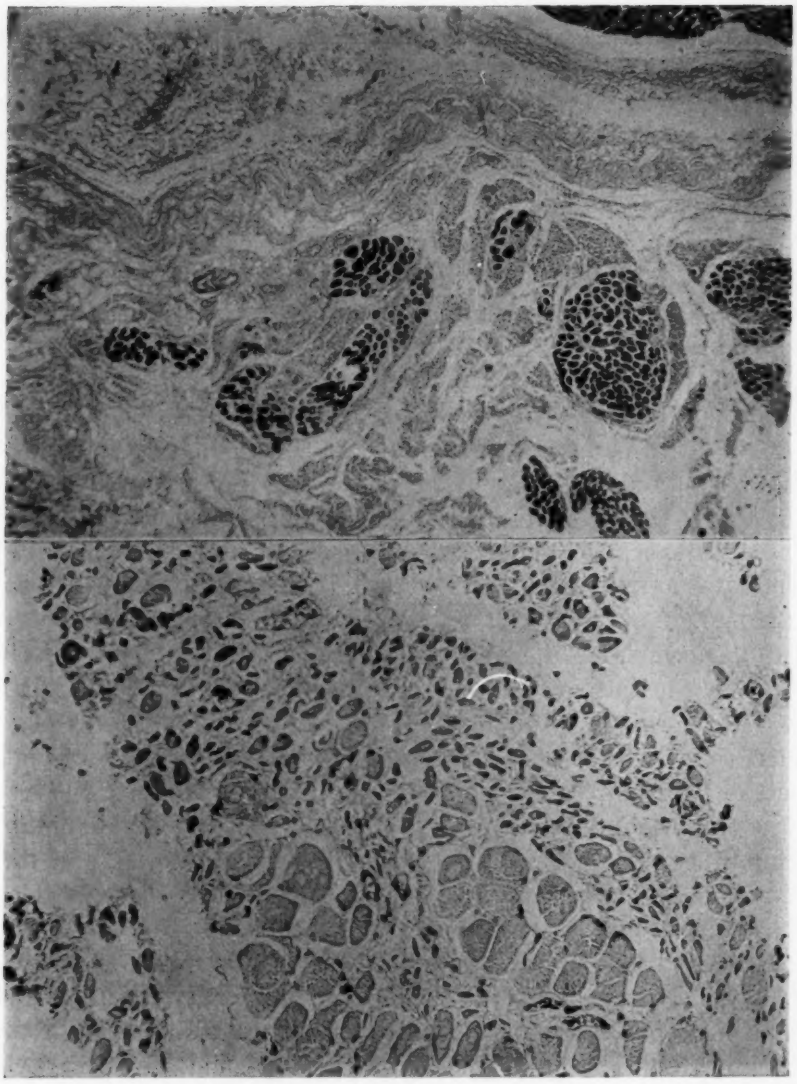

FIG. 6

FIG. 5. Section from diaphragm paralyzed by phrenicectomy, taken from the midline. Note the few histologically normal bundles scattered among atrophic fibres.

FIG. 6. Section from midline of diaphragm paralyzed by phrenicectomy. Note the sharp demarcation of normal and atrophic muscle.

the opposite side. In places the fibre lies contracted within the faintly outlined circle of the sarcolemmal sheath. The sarcoplasm is rather granular. Where the muscle fibres are cut longitudinally, the nuclei appear clumped along the sarcolemma. They vary considerably in size and shape, some globular with well-defined nuclear structure, others elongated and hyperchromatic. Many of the fibres have lost their cross-striation. There is no proliferation of the perimysial connective tissue. A number of the muscle fibres show accumulations of fat droplets of varying size. The distribution of the affected fibres is extremely irregular, scattered among structurally normal muscle with well-marked cross-striation. The interstitial adipose deposits are definitely increased and there is some fatty infiltration between the muscle fibres themselves.

The histological appearance of the diaphragms paralyzed for a period of four months or longer was quite different from that described above, the muscle for the most part having disappeared. No significant variation was noted in the type and distribution of the atrophy on the right and left sides. In places a few irregular shrunken fibres of varying size and shape are seen separated by a fine areolar network of fibrous connective tissue. Here and there in the earlier cases a fibre has retained some cross-striation. The majority however are shrunken and retracted within their sheaths, leaving a beaded chain of nuclei along the sarcolemma. These nuclei vary considerably in size and shape. The majority are small, elongated and hyperchromatic. In some areas the sheaths with their clumped nuclei are the only vestiges of muscle to be found. In others no muscle remnants can be made out, and a thin layer of areolar connective tissue, fat and serosal coverings make up the total thickness of the diaphragm. All cases show a very marked increase in the interstitial adipose deposits, and fat is everywhere to be seen infiltrating between the atrophic fibres. In the earlier cases, 4 and 14 months after phrenicectomy, fat globules are seen within many of the atrophic muscle fibres, or appear in beaded chains along the old sarcolemmal sheaths. In none of our cases were we able to detect any proliferation of the perimysial connective tissue. This observation is in accord with Lemon's (8) findings in his experimental animals, but is at variance with those of Meisezahl (1), who describes an increase of fibrous connective tissue in the paralyzed diaphragm. The diaphragmatic pleura was grossly thickened in one case only, and this was associated with a chronic inflammatory reaction. In five others there was very slight pleural thickening accompanied by a sparse inflammatory exudate of lymphocytes and plasma

FIG. 7

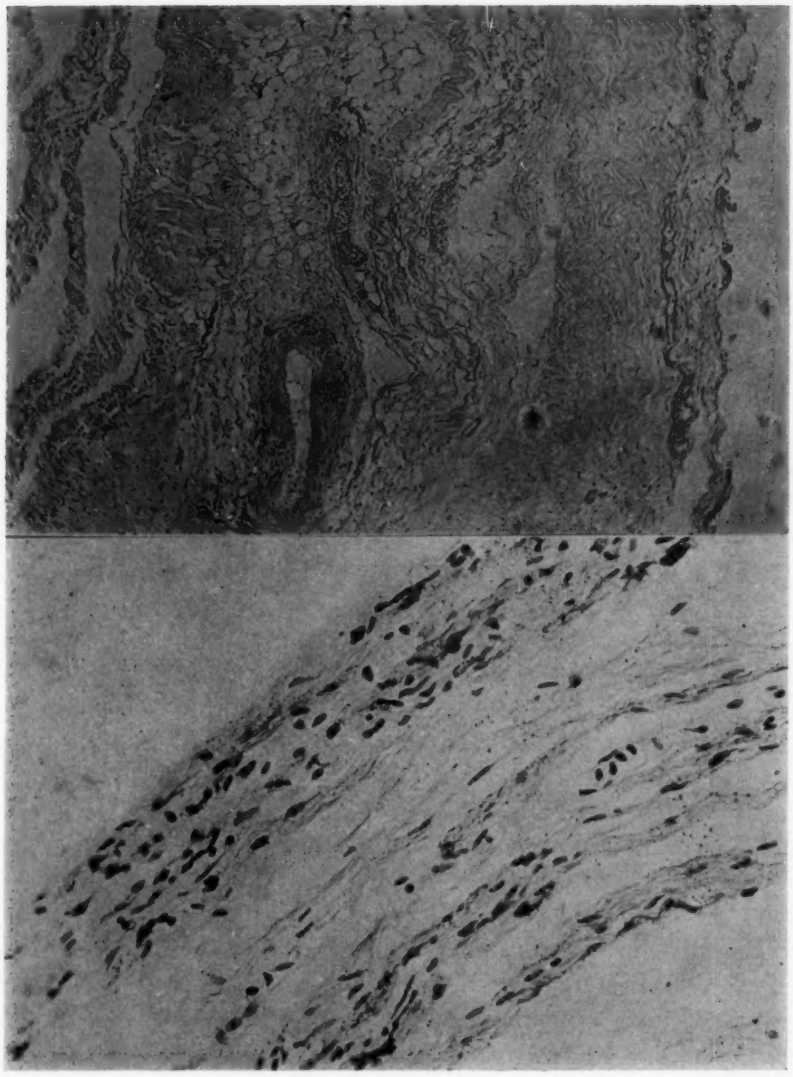

FIG. 8

FIG. 7. Section from dome of paralyzed diaphragm. Note absence of muscle fibres and the heavy deposits of fat.

FIG. 8. Section from the vertebral portion of paralyzed diaphragm. Note the clumping of nuclei along the sarcolemmal sheaths.

cells. Although some of the sections showed considerable condensation of the perimysial connective tissue about the atrophic muscle bundles, in no case could a replacement fibrosis be detected, even after six years of paralysis. Lemon (9) was unable to detect any changes in the blood-vessels in the paralyzed diaphragms of his dogs. Unfortunately he does not state over what period his animals were observed. In our series those patients whose paralysis had existed for seventeen months or longer did show a vascular change confined to the medium and small arteries of the paralyzed side. We were unable to detect any definite vascular lesion in those whose paralysis was of less than seventeen months' duration. The vessels show an intimal thickening, narrowing the lumen, and a reduplication and fragmentation of the internal elastic lamina. In some cases the media is rather hyaline in character. These changes probably form a part of an atrophy of disuse, analogous to those described by Adami (11) in the involuting uterus.

The distribution and type of atrophy were constant except for case 5 which will be discussed separately. Sections taken from the midline anterior to the oesophageal hiatus show normal muscle fibres arranged in bundles, sharply demarcated from the smaller atrophic fibres of the paralyzed side. From the midline to the periphery, the atrophy is uniform and complete. The costal digitations, particularly that to the twelfth rib, were examined with care. The atrophy in these areas is as marked as found in other portions of the paralyzed diaphragm. Sections, taken from the crus of the diaphragm on the paralyzed side where it merges with its tendinous attachment, showed a uniform atrophy in all our cases. In five of the 11 cases the margin of the oesophageal hiatus toward the paralyzed side showed a few histologically normal muscle bundles scattered among the smaller atrophic fibres. In the other 6 cases the atrophy here was as uniform and complete as elsewhere found.

Case 5 did not show the same uniformity in the distribution of atrophic change observed in the other diaphragms of the series. In the anterior portion of the sternocostal region of the paralyzed left leaf, a few histologically normal muscle bundles whose fibres have distinct cross-striations can be seen. These lie among irregular collections of atrophic muscle fibres, already described. In other portions of this diaphragm the atrophy is complete. Whether this finding represents actual regeneration of muscle or whether it can be explained by an accessory nerve fibre not evulsed at the time of operation, it is impossible to say. As has

been stated already no record is available of the type of operation performed four and one-half years before death.

Comment

With the one exception noted above, the diaphragms show no suggestion of muscle regeneration even six years after destruction of their nerve-supply. The uniform atrophy of the costal digitations, and particularly the attachment to the twelfth rib does not support the contention of Luschka (12), Pansini (13), Cavalié (14), Henle (15), Schwalbe (16), Timofejew (17), Ellenberger and Baum (18), Kappis (19), Oehlecker (20), Oppenheim (21), Walther (22), Lange (23), Morris (24), and Felix (25), that the lowest intercostal nerves send motor branches to the diaphragm in this region. If such a nerve-supply does exist, it would seem to be incapable of preventing atrophy. These findings are in agreement with the observations of Schlaepfer (6) (7), Lemon (9) and Risien Russel (26) on animals. The findings in 4 cases of our series of a few histologically normal muscle bundles scattered among atrophic fibres along the margin of the oesophageal hiatus, we are unable to explain at present. The fact that below this point toward its vertebral attachment the crus was in every case completely atrophic would suggest that a number of muscle fibres have passed around the oesophagus from the lumbar portion of the unparalyzed side. This hypothesis would seem more reasonable than the acceptance of an accessory motor nerve-supply from the sympathetic by way of the coeliac axis, as claimed by Boeke (27) and Felix (25). Schlaepfer (6) (7), and Lemon (9) found no normal muscle along the paralyzed margin of the oesophageal hiatus in their dogs. Before this question can be definitely settled, a larger series of human diaphragms, paralyzed by phrenicectomy, must be examined, with serial sections of the oesophageal region, to determine any decussation of normal muscle fibres about the hiatus.

FORM AND POSITION OF THE ABDOMINAL VISCERA

Alterations in the form and position of the stomach after phrenicectomy have been reported in the radiographic studies of Dersheid and Toussaint (28), Ricci (29), Ballon, Wilson, Singer and Graham (30) and Lichtenstein (31). Dersheid and Toussaint found morphological alterations in the stomachs of 76 per cent of their series of patients receiving left-sided phrenicectomies. Many of the gastric deformities described by these authors, and also by Lichtenstein are very marked, al-

though in no case did they encounter any serious functional disturbance. Hitzenberger (32) and Eppinger (33) have described somewhat similar alterations in the position and shape of the stomach in cases of *relaxatio diaphragmatica.*

Isolated examples of alarming gastrointestinal disturbances following phrenicectomy have been reported in the literature. While the majority of these have appeared after evulsion of the left phrenic nerve, a number have been observed after right phrenicectomy. Bernuth (34) reported the case of a girl of twelve years who was given a left-sided phrenicectomy for bronchiectasis. Five months after the operation she developed severe dyspnoea and palpitation following a heavy meal. The attack was alleviated by placing the patient in an erect posture. Further trouble was prevented by giving frequent small meals, and the patient not retiring for two hours after eating. Recently Bonafé and Poulain (35) have reported two cases of volvulus of the stomach following left-sided phrenicectomy. In one, the obstruction proved fatal in spite of operative interference. Both cases were studied radiographically. Gastric disturbances of a severe type characterized by pain after meals, gaseous distention and vomiting appeared within a month of phrenicectomy. In the fatal case a paroxysmal attack of pain and vomiting appeared six months after operation. A gastrogastrostomy was performed. The diagnosis of volvulus of the stomach was confirmed, but the patient did not survive. The second case with a similar clinical picture was relieved by gastric sedatives and the substitution of frequent small meals. The symptomatology described above bears a striking resemblance to that observed in three of our cases dying of gastroduodenal ileus.

Ten of the 11 cases of our series showed definite morphological abnormalities of the abdominal viscera. In both cases of left-sided phrenic paralysis, nos. 5 and 9, the stomach occupied a vertical position in the upper left quadrant. The cardiac portion was displaced upward and was dilated. The greater curvature was directed forward. The duodenum was displaced to the left. The small intestine lay in the pelvis. The transverse colon was not displaced upward in either case. In case 5, the stomach was tremendously dilated. In its upper two-thirds, the greater curvature pointed laterally, and in its lower third anteriorly, producing a constriction across the anterior surface of the stomach. Both loculi so formed were ballooned out and tense. The duodenum was markedly dilated for a distance of 7 cm. beyond the pylorus. On opening the stomach it was found to contain some blackish foul-smelling fluid. The

stomach-wall was thinned out and the rugae had disappeared. The duodenum contained the same type of fluid material.

TABLE 1

Analysis of 11 necropsies on cases with phrenicectomy

CASE NUMBER	AGE	SEX	NATURE OF OPERATION	RIGHT OR LEFT	DURATION OF LIFE AFTER OPERATION	HEIGHT OF PARALYZED DIAPHRAGM	EXTENT OF ATROPHY OF DIAPHRAGM	GASTROINTESTINAL COMPLICATIONS
1	45	M	Phrenicectomy (thoraco-plasty)	R	6 yrs.	4th rib	Complete	Gastroduodenal ileus
2	53	M	Phrenicectomy	R	20 mos.	4th rib	Complete	None
3	57	M	Phrenicectomy	R	4 yrs.	Upper bord. 4th rib	Complete	Gastric distortion. Marked symptoms
4	20	F	Phrenicectomy	R	14 mos.	Upper bord. 4th rib	Complete	Gastroduodenal ileus
5	35	F	Phrenicectomy (?)	L	4½ yrs.	Upper bord. 3rd rib	Partial	Gastroduodenal ileus
6	45	F	Phrenicectomy	R	4 mos.	Upper bord. 4th rib	Complete	Slight gastric distortions. Symptoms (?)
7	28	F	Phrenicectomy	R	14 mos.	Lower bord. 3rd rib	Complete	Moderate gastric distortions. Symptoms (?)
8	52	M	Phrenicectomy	R	17 mos.	Lower bord. 4th rib	Complete	Gastroduodenal ileus
9	23	M	Phrenicectomy (thoraco-plasty)	L	2 yrs.	Upper bord. 3rd rib	Complete	Marked gastroduodenal distortion with some dilatation. Asymptomatic.
10	40	M	Phrenicectomy	R	3 wks.	4th rib	Moderate	Marked gastroduodenal distortion. Symptoms ?
11	36	F	Phrenicectomy (thoraco-plasty)	R	19 mos.	3rd rib	Complete	Marked gastroduodenal distortion with some dilatation. Asymptomatic.

In the 8 cases of right-sided phrenic paralysis showing visceral deformities, the longitudinal axis of the stomach tended to lie transversely. The organ was elongated and shifted to the right to a varying degree. The fundus faced downward and the pylorus was elevated, so that it lay along the margin of the gall-bladder. Two of the stomachs presented a

uniform constriction in their midportions, giving the organ an hour-glass appearance. In three cases (nos. 1, 4 and 8) the stomach was tremendously dilated. The gastric wall was thin and the rugae were ironed out. The duodenum was very much dilated and boggy. The superior mesenteric artery was pulled tightly over the duodenal-jejunal junction and the bowel distal to it was collapsed. In case 1 a fresh gastroenterostomy wound was noted. In case 8 an old gastroenterostomy, made eight years previous to death for the relief of duodenal ulcer, was found. In case 4, the whole mucous surface of the dilated duodenum was congested and weeping blood. There was no evidence of ulceration. In each of these cases the small intestine was down in the pelvis.

There was no quantitative relationship between the elevation of the paralyzed diaphragm and the degree of visceral deformity in the present series.

As has been stated already, 4 cases of our series died, not as the result of their tuberculous disease, but of gastroduodenal ileus. We may disregard case 8, as it is complicated by previous gastrointestinal disorders. There remain 3 cases (nos. 1, 4 and 5), characterized clinically by gastrointestinal complaints appearing after phrenicectomy, and death from an acute upper intestinal obstruction. In each case the severity of the clinical manifestations was out of all proportion to the activity of the tuberculous lesion. In none were any of the well-recognized causes of obstruction demonstrable at necropsy. In one case only was the diagnosis made clinically (case 1). The usual medical measures of gastric lavage, knee-chest position and antispasmodics failing to give relief, a gastroenterostomy was done. The patient however failed to respond, dying the day following. Gastrointestinal complaints, accompanied by periodic attacks of paroxysmal abdominal pain and vomiting over a four-year period were the characteristic features of case 5. Clinically this was thought to be due to tuberculous enteritis, but careful study of the bowel with numerous microscopic sections failed to show any tuberculous involvement. Case 4 presented a similar clinical picture, with abdominal pain of a crampy character, nausea, vomiting and extreme shock. For several days before death the patient had considerable diarrhoea with blood in the stools. The condition was thought to be due to tuberculous enteritis. At postmortem a single minute tuberculous ulcer was demonstrated on the ileocaecal valve. The stomach and duodenum have been described above.

It is not the purpose of this paper to discuss the frequency or nature of

gastrointestinal complications following phrenicectomy. From our series at this sanatorium it would be impossible to make any accurate estimate, the majority of the operations having been done during the past two years. Our observations on the shape and position of the abdominal viscera are essentially in agreement with those of Hitzenberger (32) and Eppinger (33) in *relaxatio diaphragmatica*, and are comparable with the radiographic descriptions of Dersheid and Toussaint (28), Ricci (29) and Lichtenstein (31) after phrenicectomy. Whether section of the phrenic nerve and the resulting paralysis of the diaphragm bear a causal relationship to acute upper intestinal obstructions, such as reported by Bonafé and Poulain (35) and described by us in the present communication, must await further investigation.

Comment

The factors involved in the production of such marked deformities of the abdominal viscera, as observed by ourselves and others, cannot be considered as settled. Bonafé and Poulain (35), and Dersheid and Toussaint (28), believe the explanation to be entirely mechanical, in that the elevation of the diaphragm leads to an alteration in the position and tension of the peritoneal supports of the stomach. Berlin (36) in the report of a single case, presenting gastrointestinal symptomatology after right-sided phrenicectomy, states his belief that this may be explained by injury to the coeliac plexus. He is of the opinion that such trauma to the sympathetic-nerve supply, as might be occasional by phrenic evulsion, is capable of causing loss of tone in the gastric musculature, with consequent dilatation of the organ. Jackson (37), Mosher and McGregor (38), and Joannides (39) (40), have called attention to the intimate relationship between the crura of the diaphragm and the gastroöesophageal juncture. Mosher and McGregor were unable to demonstrate any intrinsic oesophageal sphincter. It is their opinion that the crura of the diaphragm act in this capacity. If the observations of these investigators are correct, this factor must also be taken into account in the genesis of gastric disturbances following phrenicectomy. Ballon, Wilson, Singer and Graham (30) have demonstrated changes in the form and position of the oesophagus after left-sided phrenicectomy. These authors do not consider such alterations as they observed to be of any clinical significance. Kelling (41) found, in his experimental work on acute dilatation of the stomach, that some anatomical or physiological interference with the sphincter at the lower end of the oesophagus must be associated with

the frequently recognized duodenal obstruction, before dilatation could result.

While no definite conclusions can be drawn as to the mechanisms involved, the eventration of the diaphragm following phrenicectomy does lead to an increase in the size of the abdominal cavity. The consequent readjustment of the viscera may produce a tension and even torsion of their mesenteric attachments. It is quite possible that each of the factors mentioned above, either singly or in combination, might play a part in the production of visceral deformities. Moreover, the marked visceroptosis so frequently observed in the chronic invalid, and noted to a varying degree in all our cases, well may be a factor in complicating otherwise asymptomatic sequelae to paralysis of the diaphragm.

SUMMARY

1. An analysis is given of 11 cases of atrophy of the diaphragm following section of the phrenic nerve. In all but one case the operation of choice was evulsion by the method of Felix. The duration of the paralysis noted in the series varied from three weeks to six years.

2. Atrophy of the diaphragm is evident as early as the third week after section of the phrenic nerve and is complete by the fourth month.

3. After paralysis one-half of the diaphragm is elevated and eventrated into the thorax. With stretching it becomes a thin whitish membrane of parchment-like thinness.

4. Histologically the atrophy of the paralyzed half of the diaphragm is seen to be complete and uniform. In one case only, a few normal muscle bundles are seen in one area, scattered among atrophic fibres. This probably represents an accessory nerve-supply, rather than actual regeneration.

5. In view of the marked distortion of the abdominal viscera in ten of the 11 cases, three of which had a fatal gastroduodenal obstruction, the possibility of such complications must be considered seriously when advising phrenicectomy for the treatment of pulmonary disease.

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THE CORRELATION OF SHIFTING ELECTRICAL AXIS OF THE HEART WITH X-RAY OBSERVATIONS IN ARTIFICIAL PNEUMOTHORAX[1]

I. TREIGER AND C. J. LUNDY

Although artificial pneumothorax is one of the standard methods of treatment in pulmonary tuberculosis, the literature describing electrocardiographic changes under this treatment is very meagre. The gross changes found are variations in direction of QRS in leads one and three. Increased or decreased voltage of QRS in all leads is also found, and in some cases voltage of QRS diminishes to less than 0.5 mv. in one lead, usually the first or third. The conclusions drawn from these observations are contradictory and various explanations have been made for the changes observed.

We undertook the present investigation in order to help clarify this situation. Our studies deal with shifting of the electrical axis of the heart, measured by Einthoven's "triangle" (1), in correlation with X-ray observations on the positional changes of the heart. The results were compared with gross electrocardiographic changes found in our cases.

METHOD

Thirty-one cases were studied, 17 with left and 14 with right pneumothorax. They were unselected, being picked at random out of a rather large number of pneumothorax cases. Electrocardiograms and X-rays were taken on all patients before and at various intervals during pneumothorax therapy. As many as 10 electrocardiograms and 40 X-ray observations were made in a single case. The electrical axis in each electrocardiogram was measured and projected on Einthoven's triangle; in this manner the direction and exact degree of shifting were determined.

Some cases were studied during and immediately after gas administration, but special attention was given to studies made over a long period of time—up to three and one-half years while the patient was under treatment. During these studies a number of complications arose and were taken into consideration for a proper interpretation of the results. These included variations in the quality of pneumothorax, fluid in the pleural

[1] From the Municipal Tuberculosis Sanitarium and Rush Medical College, Chicago, Illinois.

*Tabulated Findings**

CASE NUMBER	DATE	SHIFTING OF ELECTRICAL AXIS	DISPLACEMENT OF HEART	QUALITY OF PNEUMOTHORAX	ADHESIONS	FLUID
			Left Pneumothorax			
290	5- 1-29	82	Normal position	None	None	None
	5-24-29	82	Same	Poor	None	None
72	9-19-28	52	Normal position	None	None	None
	10-10-28	71	Same	Partial, good	None	None
	12-12-28	69	Slightly right	Partial, good	None	None
211	1-17-29	58	Normal position	None	None	None
	1-24-29	79	Same	Fair	None	None
	1-30-29		Slightly to right	Good	None	None
209	1-18-29	28	Normal position	None	None	None
	3-11-29	57	Right	Excellent	None	None
521	11-11-31	16	Normal position	None	None	None
	1-13-32	69	Right	Excellent	None	None
75	9-24-28	45	Normal position	None	None	None
	10- 2-28	57	Same	Partial	None	None
	12-13-28	62	Right	Partial, good	None	None
	5-27-29	02	Left to normal	Partial, excellent	Left lung, base	None
204	1-15-29	12	Normal position	None	None	None
	3-18-29	22	Slightly to right	Fair, partial irregular	None?	None
	12- 9-31	16	Left to normal	Fair	Left lung, base	None
233	2-19-29	75	Left of normal	None	None	None
	2-20-29	78	Slightly right to normal position	Fair	None	None
	2-13-30	84	Slightly right of normal position	Excellent	None	Left lung, base
345	9-18-29	7	Normal position	None	None	None
	9-21-29	67	Slightly to right	Good	None	None
	10- 1-29	74	More to right	Excellent	None	None
	2-26-30	58	Slightly to right	Excellent, partial		Left lung, base
	12-23-31	33	Left to normal	Fair	Haziness, left lung, base	Left lung, base, haziness
347	9-23-29	81	Normal position	None	None	None
	3- 4-30	81	Same	Fair	Cardiac apex	None
274	4-10-29	59	Left of normal	None	None	None
	6-27-29	(No EKG)	Right	Excellent	None	None
	2- 7-30	62	Left to original position	Excellent	Left lung, base	None
210	1-18-29	65	Normal position	None	None	None
	3-11-29	63	Right	Excellent	None?	None
	11- 1-29			Discontinued, adhesions		
256	3-27-29	74	Normal position	None	None	None
	3-29-30	72	Right	Excellent	None?	None
	4- 5-30			Phrenic operation, adhesions		
311	6-14-29	97	Normal position	None	None	None
	7- 1-29	86	None	Poor	None?	None
	4-21-30			Autopsy showed many adhesions		
353	10-16-29	57	Slightly left of normal position	None	None	None
	10-23-29	47	Slightly right	Poor	Numerous	None
	2-26-30	13	Left	Very poor	Numerous	None
283	4-18-29	78	Left of normal	None	None	None
	6- 5-29	39	Slightly to right	Partial	None	None
	2-25-30	70	Same as 6-5-29	Good	None?	None
	4-12-30			Phrenic operation, adhesions		

Tabulated Findings—Concluded

CASE NUMBER	DATE	SHIFTING OF ELECTRICAL AXIS	DISPLACEMENT OF HEART	QUALITY OF PNEUMOTHORAX	ADHESIONS	FLUID
			Left pneumothorax—Concluded			
8	8-15-28	95	Slightly left of normal position	None	None	None
	8-20-28	75	Slightly right	Good	None	None
	9-12-28		Same	Partial	Left lung, mid-region	None
	2- 7-30	63	Obscured	Poor	Left lung, mid-region	Entire left side
			Right Pneumothorax			
431	7- 7-31	71	Normal position	None	None	None
	1- 2-32	69	Same	Fair	None	None
253	3-22-29	56	Normal position	None	None	None
	4- 1-29	58	Same	Poor	None	None
177	12-18-28	86	Normal position	None	None	None
	12-18-28	92	Same	Poor	None	None
278	4-13-29	37	Right of normal position	None	None	None
	4-23-29	47	Left to normal position	Good	None	None
224	1-26-29	50	Right of normal position	None	None	None
	3- 8-29	65	Left to normal position	Good	None	None
107	10-17-28	65	Right of normal position	None	None	None
	10-22-28	80	Slightly to left	Good	None	None
192	12- 3-28	7	Right of normal position	None	None	None
	6-12-29	23	Slightly to left	Poor	None	None
219	1-31-29	1	Normal position	None	None	None
	1-31-29	23	Same	Good	None	None
	3- 2-29	18	Slightly to left	Excellent	None	None
467	8-12-31	40	Normal position	None	None	None
	5-18-32	77	Left	Excellent	None	None
243	3- 5-29	66	Slightly right of normal position	None	None	None
	3-14-29	77	Same	Poor	None	None
	6- 3-29	72	Same	Poor	Numerous	None
291	5- 1-29	59	Right of normal position	None	None	None
	5-13-29	80	Left to normal position	Excellent	None	None
	2-13-30	45	Right of normal position	Partial, fair		Haziness, right lung, base
277	4-13-29	3	Normal position	None		Haziness, right base
	6- 7-29	−16	Same	Fair, partial		Less haziness
	3-27-30	34	Same	Fair	None	None
323	7- 3-29	11	Normal position	None	None	None
	2-19-30	13	Left	Good, partial		Right lung, base
310	6-11-29	45	Right of normal position	None	None	Right lung, base
	6-17-29	53	Left not to normal	Fair		Less lung, base

* The first date in each case is the date when electrocardiagram and X-ray have been taken before pneumothorax. Other dates are during pneumothorax. In order to avoid confusion, repetition, and a complicated table, we have not given all the findings in every case during pneumothorax; only the significant changes are recorded.

In each case the shifting of electrical axis was found by electrocardiographic study. X-ray studies gave us information in regard to displacement of the heart, quality of pneumothorax, adhesions and fluid.

cavity, adhesions on the pneumothorax side, and pathological involvement of the opposite lung with or without adhesions, all of these causing changes in heart position or electrical axis.

FINDINGS

The cases were separated into two groups of left and right pneumothorax. These were divided into three subgroups: (1) uncomplicated cases (without adhesions or fluid); (2) cases with adhesions; and (3) cases with fluid.

1: Uncomplicated cases (without adhesions or fluid): Out of 17 left-pneumothorax cases, 9 were studied before adhesions or fluid developed. Of these 9, one (no. 290) showed no changes and had a very poor pneumothorax; 8 showed a varying degree (9° to 77°) of shifting of the electrical axis to the right, which depended upon the quality of the pneumothorax. The average shifting was 27° to the right. X-ray observations showed displacement of the heart to the right which was not in proportion to the degree of shifting of the electrical axis.

Out of 14 right-pneumothorax cases, 11 were studied before adhesions or fluid developed. Of these eleven, 3 (nos. 177, 253, and 431) showed little or no change and had a poor or fair pneumothorax; and 8 showed a varying degree (8° to 37°) of shifting of the electrical axis to the right depending on the quality of the pneumothorax. The average shifting was 14.5° to the right. X-ray observations showed displacement of the heart to the left, independent of the shifting electrical axis.

The average shifting of the electrical axis to the right was greater in left than in right pneumothorax. The degree of shifting of the axis is in direct proportion to the quality of pneumothorax. An excellent and complete pneumothorax causes a much greater shifting to the right than a poor and partial one. When pneumothorax injection is given for the first time, there is quick absorption of the injected air and frequently poor or partial pneumothorax. In so-called selective pneumothorax, the gas is given at first in smaller quantity and at more frequent intervals than later on. In such cases the shifting may be absent or very slight, and will increase later on when pneumothorax is well established.

Other factors, besides the quality of uncomplicated pneumothorax, which possibly could affect the shifting of the electrical axis are the position of the heart before pneumothorax and organic heart disease. The heart may be in normal position or displaced by pathological processes in the lung: in left-lung involvement it is usually displaced to the left; in right-lung involvement, to the right. In left-pneumothorax cases when the disease is usually in the left lung, the heart may be found in

normal position or displaced to the left before treatment is begun; in right-pneumothorax cases it may be found in normal position or displaced to the right. In this study we observed no noticeable influence of the position of the heart before pneumothorax on the shifting of the electrical axis during pneumothorax.

There was only one case (no. 290) of heart disease present before pneumothorax. This patient was

a colored woman, 29 years of age, with far-advanced tuberculosis of the entire left lung and with cavities. She also had a severe diabetes mellitus and a considerably enlarged heart. During pneumothorax there were observed no changes in heart position or shifting of the electrical axis. Pneumothorax, of poor quality, was given for two months and discontinued. Three months later the patient died. Autopsy verified the clinical diagnosis.

Obviously, a single case does not permit the drawing of conclusions as to the influence of heart disease on shifting of the electrical axis during pneumothorax therapy.

There was no evidence that diminished pulmonary circulation had, as a result of pneumothorax, in any manner influenced the shifting of the electrical axis in these cases.

2: Pneumothorax cases with adhesions (developed while under treatment): Ten of the 17 left-pneumothorax cases developed adhesions while under treatment. In 9 the adhesions were near the apex of the heart, that is, in the base of the left lung, and in one the adhesions were near the base of the heart in the mid-region of the left lung. Of these 10, two had electrocardiograms before and after adhesions developed, and 8 were studied only after adhesions appeared.

Adhesions near the apex of the heart (base of left lung) in these left-pneumothorax cases were associated with both a shifting of the electrical axis and displacement of the heart to the left. This is in contradistinction to left pneumothorax before adhesions developed, which shifted the electrical axis and displaced the heart to the right. After adhesions develop the shifting of the electrical axis and displacement of the heart is to the left, back toward the position before pneumothorax or even beyond this position still more to the left. The one case with the adhesions near the base of the heart (mid-region of the left lung) was also associated with a shifting of the electrical axis and displacement of the heart to the left. We do not attempt to draw conclusions concerning this single instance.

The degree of shifting of the electrical axis to the left in left pneumo-

thorax with adhesions near the cardiac apex is in direct proportion to the quantity and quality of adhesions, which in turn influence the quality of pneumothorax. The shifting to the left is greater when the adhesions are numerous, strong, and cord-like, and when pneumothorax is partial and of poor quality. The degree of shifting to the left is less when adhesions are few and weak and when pneumothorax is excellent and more complete. The adhesions interfere with the quality of pneumothorax and change it from complete and excellent into partial and of lower grade. The location of the adhesions is important since the adhesions in the base of the lung have their main influence on the cardiac apex.

Only one case (no. 243) of right pneumothorax with adhesions was observed. This case showed shifting of the electrical axis to the right with no gross change in the heart position after pneumothorax but before adhesions developed. After adhesions appeared, the electrical axis shifted slightly to the left and the heart position still remained unchanged. There was poor pneumothorax throughout the period of observation. No attempt is made to draw conclusions about this single case, but it should be considered together with the cases of right pneumothorax with fluid and adhesions.

3: Pneumothorax with fluid: These cases are considered separately since they introduce a third factor which might influence the effect of pneumothorax on the electrical axis of the heart.

There were 3 left-pneumothorax cases with fluid. Case 8 showed shifting of the electrical axis to the left while the heart was displaced slightly to the right. Later the heart position became obscured because of the fluid, but it remained in the left chest. Adhesions were seen in the mid-region of the left lung (near the base of the heart). There is no clear evidence that there were no adhesions near the cardiac apex causing the results to agree with that group. This single case cannot be used for drawing conclusions about the influence of adhesions at the base of the heart. Before fluid developed case 345 showed shifting of the electrical axis to the right, together with displacement of the heart to the right and an excellent pneumothorax. After fluid developed in the base of the left lung the electrical axis rotated 41° to the left and the heart was displaced left, back to its normal position, while the pneumothorax changed from excellent to partial and fair. Case 233 showed shifting of the electrical axis to the right and displacement of the heart to the right. After fluid developed the axis shifted still more to the right and the heart was displaced still further to the right, but the pneumothorax became excellent.

There were 4 right-pneumothorax cases with fluid. Case 291 showed

shifting of the electrical axis to the right and displacement of the heart to the left during pneumothorax, but before fluid developed. After fluid appeared the axis shifted left and the heart moved to the right while an excellent pneumothorax became partial and fair. Case 277 showed shifting of the electrical axis to the left after a fair but partial pneumothorax with a diminished amount of fluid (compared with control observation before pneumothorax). Later, when the fluid disappeared and the pneumothorax became fair and more complete, the electrical axis shifted 50° to the right. The heart position remained unchanged throughout. Case 323 showed no shifting of the electrical axis and some displacement of the heart to the left with a good but partial pneumothorax after fluid appeared in the right lung base. Case 310 showed shifting of the electrical axis slightly to the right and displacement of the heart position to the left with a fair pneumothorax, after fluid in the right lung base had diminished.

Fluid in pneumothorax cases, similar to adhesions, influences the quality of pneumothorax and frequently changes it from complete and excellent into one of partial and lower grade. Adhesions frequently develop, especially after partial absorption of fluid, and their action may overcome the two other factors—pneumothorax and fluid. Since adhesions frequently develop in fluid cases and since the electrical axis shifts to the left when fluid complicates the pneumothorax, we conclude that in some instances the shifting may be due to the adhesions. We found evidence of adhesions or fluid in every case which showed shifting of the electrical axis to the left under pneumothorax therapy regardless of the side into which the gas was administered. Three cases, nos. 233, 310 and 323, showed very slight shifting of the electrical axis to the right during pneumothorax, and we attribute this fact to the influence of adhesions or fluid or both in not quite counterbalancing the influence of the pneumothorax.

The degree of rotation of the electrical axis to the left depends upon three factors: (1) quality of pneumothorax; (2) quantity and quality of adhesions; and (3) the quantity of fluid. The degree of pneumothorax is a good index for determining the influence of adhesions and fluid, since they diminish its quality and quantity when sufficient to change the usual results. Left pleural effusion in left pneumothorax in two out of three cases was associated with shifting of the electrical axis to the left. In one of these cases, no. 8, the influence of adhesions may have played a part in this shifting; in the other, no. 345, adhesions may have played a part later, but before they could have developed to any great extent shifting of the axis to the left had occurred with the appearance of fluid. The

third case, no. 233, had an excellent pneumothorax together with fluid in the left lung base associated with only a little (9°) shifting to the right. We believe that fluid in the left pleural cavity is associated with shifting of the axis to the left, and that in this case it was not sufficient to completely reverse the usual result secured in uncomplicated left pneumothorax.

In right pneumothorax 2 cases showed shifting of the axis to the right as a right pleural effusion diminished, in the presence of a fair pneumothorax. In one case (no. 277) the fluid entirely disappeared and no adhesions were seen. In this case especially do we think is shown the effect of right pleural effusion in right pneumothorax, and we consider this to be a shifting to the left. This is further borne out by case 291, which shifted to the right before fluid developed and after pneumothorax of excellent quality, and then rotated left after fluid developed and pneumothorax diminished. Case 323 failed to shift right after a good pneumothorax in the presence of fluid in the right lung base. Thus the results show that pleural effusion independent of, as well as in association with, demonstrated adhesions, is associated with shifting of the electrical axis to the left in both left and right pneumothorax.

GROSS CHANGES IN SHIFTING OF THE ELECTRICAL AXIS

A grossly normal axis before treatment was found in 11 cases out of 17 with left pneumothorax and in 10 cases out of 14 with right pneumothorax. During treatment these QRS complexes remained upright, but showed increase or decrease of voltage. Gross axis deviation present before treatment was found in 10 cases. Left pneumothorax included 4 cases of left- and 2 cases of right-axis deviation. Right pneumothorax included 4 cases of left- and no cases of right-axis deviation. During pneumothorax all of these cases showed changes of the electrical axis which, upon gross inspection, were not uniform.

Low voltage, less then 0.5 mv., in lead one was observed in 13 of the 17 left-pneumothorax cases. Four of these were of low voltage before and remained so during pneumothorax. Nine of these were normal before and of low voltage during pneumothorax. Low voltage of QRS in lead one was not observed in any right-pneumothorax cases. Low voltage of QRS in lead three was present before treatment in 3 left and 3 right pneumothoraces. All of these cases developed normal voltage during pneumothorax. In both instances, when low voltage of QRS appeared in lead one and when low voltage of QRS in lead three returned to normal voltage, these changes accompanied shifting of the electrical axis to the right when determined by computation.

The gross changes gave us an approximate, but often incorrect, estimation of the direction of shifting of the electrical axis. Measurement of the QRS complexes revealed changes not apparent on gross examination and showed us more correctly the direction of shifting, but only by the use of the Einthoven triangle were we able to determine the exact degree of shifting and this method gave us rather uniform results.

We will cite in detail one case which shows the error which can arise in this manner:

Case 345: Left pneumothorax which developed adhesions and fluid after five months' treatment. Before pneumothorax was induced, X-ray showed the heart to be in normal position; no adhesions or fluid present. The electrocardiogram on gross inspection appeared to show left-axis deviation, but upon computing the electrical axis it was found to be plus 7°—entirely within normal limits. Excellent pneumothorax gradually displaced the heart until it was completely within the right pleural cavity. Gross inspection of the electrocardiogram revealed a normal axis with low voltage of QRS in lead one which agreed with the computation of plus 74°; that is, it had shifted 67° to the right. On February 26, 1930, fluid was found to have appeared in the base of the left lung; the pneumothorax had become only partial; the heart had been displaced to the left; and the electrical axis was plus 58°, that is, it had shifted 16° to the left. Gross inspection of the electrocardiogram did not reveal this shifting of the electrical axis. On December 23, 1931, adhesions had pulled the heart still more to the left, apparently to its original position and the computed electrical axis was plus 33°; that is, 25° more to the left and still there was no gross indication of return to the original left-axis deviation seen in the control electrocardiogram before pneumothorax.

DISCUSSION

Hubert Mann (2) expresses briefly his opinion in regard to changes in the direction of the cardiac axis, citing three possibilities:

First: The cardiac axis may be approximately unchanged, due either to the retention of the heart in its normal position by adhesions or to the symmetrical displacement of all parts of the heart. In this case the electrocardiogram will be approximately unchanged by the pneumothorax.

Second: The cardiac apex is relatively more displaced than the base; the cardiac axis may become more vertical. The electrocardiogram will approach the type known as right ventricular preponderance.

Third: Due to a relatively greater displacement of the base and a fixation of the apex by adhesions or by the natural ligaments, the cardiac axis may become more horizontal. The electrocardiogram will approach the type known as left ventricular preponderance.

This opinion explains some of our findings, while a number of them needed a more complete and detailed explanation, which we are attempting to give at this time.

The anatomical position of the heart in relation to the lungs is such that the left lung is in direct contact with the left base and apex of the heart, while the right lung is in direct contact only with the right base of the heart. The anatomical axis is the oblique diameter of the cardiac ovoid, which extends from the base to the apex of the heart. The cardiac base is more or less fixed by the great vessels which permits the apex to be more freely moveable than the base.

In uncomplicated left pneumothorax, pressure is exerted equally upon the base and apex of the heart, but the apex, being more freely moveable, is relatively more displaced to the right than the base. The electrical axis becomes more vertical and is shifted in a clockwise direction, to the right. In uncomplicated right pneumothorax, pressure is exerted almost entirely upon the cardiac base and upper part of the cardiac axis. In this manner the axis also becomes more vertical and rotates in a clockwise direction, shifting to the right. This explains the seemingly paradoxical shifting of the electrical axis to the right in right pneumothorax when X-ray shows the heart displaced to the left. It is noticed that the average shifting of the axis to the right is greater in left than in right pneumothorax. This also is readily explained, since left pneumothorax has a direct action on the more freely moveable cardiac apex while right pneumothorax acts directly upon the less freely moveable cardiac base.

The presence of adhesions introduces a new factor, which alters the influence of uncomplicated pneumothorax according to their location, quantity and quality. Left-sided adhesions in the region of the cardiac apex may interfere slightly with or prevent entirely the displacement of the cardiac apex, as occurs in uncomplicated left pneumothorax. If the adhesions are very numerous and cord-like they may even pull the cardiac apex to the left. The result of the action of adhesions in this site will be to shift the axis to the left or to oppose shifting of the axis to the right, thereby diminishing or neutralizing the influence of left pneumothorax. The end-result will be a summation of these two influences—left pneumothorax and adhesions near the cardiac apex. We studied only one case with adhesions near the cardiac base and it may have had adhesions at the apex in addition. We offer the suggestion that adhesions in this region will similarly immobilize the base still more, or fix it in an immoveable position, or even pull it to the left. In all three circumstances the axis will tend to shift to the right still more than is seen in uncomplicated left pneumothorax. Since the cardiac apex lies in the left pleural

cavity, right-sided adhesions can only attach themselves to the base of the heart. Under these circumstances the base may be pulled to the right, or the adhesions will interfere with right pneumothorax displacing the base to the left in all instances, causing the heart to remain more horizontal, thereby being associated with shifting of the axis to the left.

Pleural effusion introduces a third factor, which plays a part in influencing shifting of the electrical axis in artificial pneumothorax. It would be logical to expect that the action of fluid would be similar to, and would reinforce the action of, uncomplicated pneumothorax. The opposite was the result, these cases all showing shifting to the left when sufficient to interfere with the quality of the pneumothorax. It certainly is true that in both left and right pneumothorax with fluid the result could be attributed in most cases to the simultaneous presence of adhesions. However two cases showed shifting of the axis to the left in the presence of the fluid which shifted to the right when the fluid diminished. In one of these cases the fluid completely disappeared and there were no adhesions seen which could have influenced the result.

SUMMARY

1: Artificial pneumothorax, without adhesions or fluid, whether left or right, shifts the electrical axis to the right. The heart is displaced to the right by left pneumothorax and to the left by right pneumothorax. This displacement may be independent of the shifting of the electrical axis.

The degree of shifting of the electrical axis in pneumothorax is in direct proportion to the quality of the pneumothorax. The average shifting of the axis to the right is greater in left than in right pneumothorax.

2: Adhesions in pneumothorax may prevent the usual shifting of the electrical axis to the right, in whole or in part, and may be associated with shifting of the electrical axis to the left.

The degree of axis-shifting in pneumothorax with adhesions is influenced by the location, quantity, and quality of adhesions as well as by the quality of pneumothorax. Adhesions usually prevent the production of a complete and excellent pneumothorax and are associated with a partial pneumothorax of lower grade, thus diminishing or eliminating the factor of pneumothorax.

3: Fluid in pneumothorax, similar to adhesions, frequently is associated with shifting of the electrical axis to the left. This may be due to the presence of adhesions. However, it was seen that fluid without demonstrated adhesions also was associated with shifting of the axis to the left.

Fluid in pneumothorax, similar to adhesions, influences the quality of pneumothorax and frequently changes it from complete and excellent into one of partial and of lower grade. Adhesions frequently develop, especially after a partial absorption of fluid, and their action may overshadow the two other factors—pneumothorax and fluid.

CONCLUSIONS

1. Artificial-pneumothorax cases, with or without adhesions and fluid, show various gross changes in the direction of QRS in the first or third leads and increase or decrease in voltage of QRS in leads one, two, and three. A decrease in voltage of QRS in one of the leads, usually the first or third, may make QRS of that lead less than 0.5 mv.

2. These gross changes are approximate manifestations of shifting of the electrical axis and are subject to considerable error.

3. The correct direction and degree of shifting can only be found by measurement of the QRS complexes and projection upon Einthoven's triangle.

4. Uncomplicated pneumothorax, left or right, shifts the electrical axis to the right. The degree of shifting depends upon the quality of the pneumothorax. The heart is displaced to the right by left pneumothorax and to the left by right pneumothorax.

5. Pneumothorax, complicated by adhesions or fluid, may shift the electrical axis to the left. The degree of shifting depends upon the location, quantity, and quality of the adhesions and upon the quantity of fluid.

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A PORTABLE ARTIFICIAL-PNEUMOTHORAX APPARATUS[1]

EMIL BUNTA

The portable apparatus[2] described herein was designed by the author for use at the bedside. It embodies certain mechanical improvements based on a personal experience of over 2,500 pneumothorax injections.

This instrument consists of three units, the siphonage system, the air- or gas-unit (a device for the conveyance of either atmospheric air or nitrogen gas to the free pleural cavity), and a manometer with a central water reservoir.

For siphonage purposes the set includes two rectangular shaped, graduated glass bottles (*A*) and (*B*), each having a capacity of 1000 cc. and connected by glass and rubber tubing with an intermediate stopcock (*S5*) as shown in the diagram. The containers, one in an elevated position, hold a 1 to 2,000 phenol solution.

A maximum air displacement of 800 cc. is available through siphonage, the rate of which may be accelerated, as desired, by pumping air into bottle *A*. The fluid-levels in the two bottles can be reversed by pumping air into bottle *B* by way of stopcocks (*S3, 4, 7*), the last one of which simultaneously shuts off communication with the outgoing portion of the air-tube. Should more than 800 cc. of air be required for collapse purposes, utilization of the by-pass (*S7*) permits resiphonage without detaching the air-tube from the needle.

The air or gas unit comprises an air-chamber (*B*) and air-tube connected to the stopcocks (*S2, 3, 4*) in series with the manometer. Distally, in the path of the air-tube is a two-way stopcock (*S8*). A rubber tube connects one arm of the stopcock to a glass tube extending into 200 cc. of a 25 per cent pyrogallic-acid solution in bottle *C*. Attached to the other arm of stopcock *S8* is a rubber tube which is connected to the left arm (*L*) of the two-way stopcock (*S6*). The right arm (*R*) of the latter is fitted by rubber tubing to a glass tube which communicates with the space above the liquid in container (*C*). Joined to the outgoing arm of stopcock (*S6*) is a five-foot rubber tube leading to the needle.

The atmospheric air displaced by siphonage may be utilized in one of

[1] From the Pneumothorax Clinic, Municipal Tuberculosis Clinic, Chicago, Illinois.

[2] Photograph (Fig.1) by Edward Weis, X-ray Technician, Municipal Tuberculosis Sanitarium, Chicago.

two ways. By manipulating both stopcocks (*S6*) and (*S8*), air may be conveyed directly to the pleural cavity; or shunted into bottle (*C*), thus allowing the air to pass through the pyrogallic-acid solution which absorbs oxygen from the air and releases nitrogen. When the oxygen-absorbing power of this solution is diminished a fresh supply may be substituted.

Irrespective of the relative merits of air or nitrogen gas for the induction of artificial pneumothorax, passage of atmospheric air through a

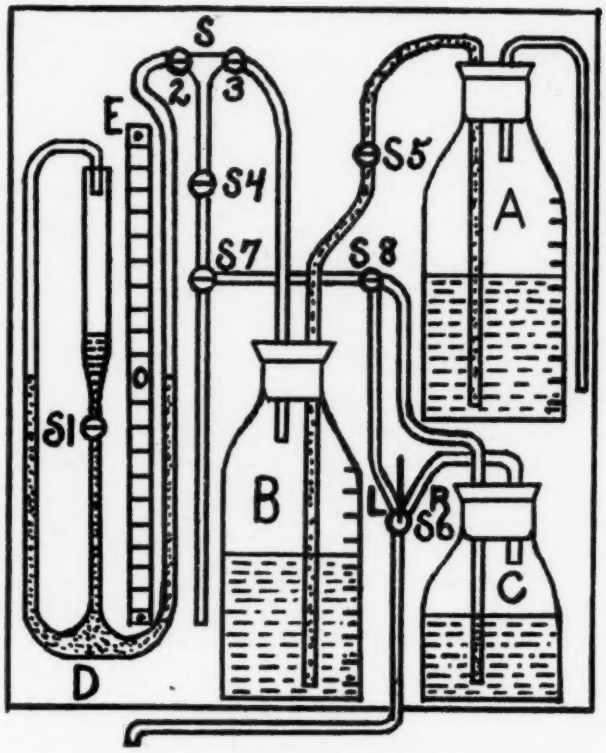

DIAGRAM 1. INSTRUMENT PANEL

For description see text

pyrogallic-acid bath provides safety against the transference of contaminated dust to the pleura.

The container holding this liquid also acts as a trap to intercept any manometer fluid aspirated into the air-tube by an excessive negative intrapleural pressure; or pleural fluid forced from the chest into the air-tube incident to a sudden rise of intrathoracic pressure.

The manometer (*D*) includes an inner and outer tube having a bore

3 mm. in diameter and 30 cm. in length. A glass burette and stopcock (*S1*), serving as a water reservoir, 12 cm. long and 14 mm. in diameter, is centrally situated and joined by glass tube with the bend. The inner arm is fitted to stopcock (*S2, 3, 4*), and the open end of the outer arm dips into the top of the burette. A scale (*E*) graduated in centimetres, 11 above and 11 below zero level, lies adjacent to the proximal tube of the manometer.

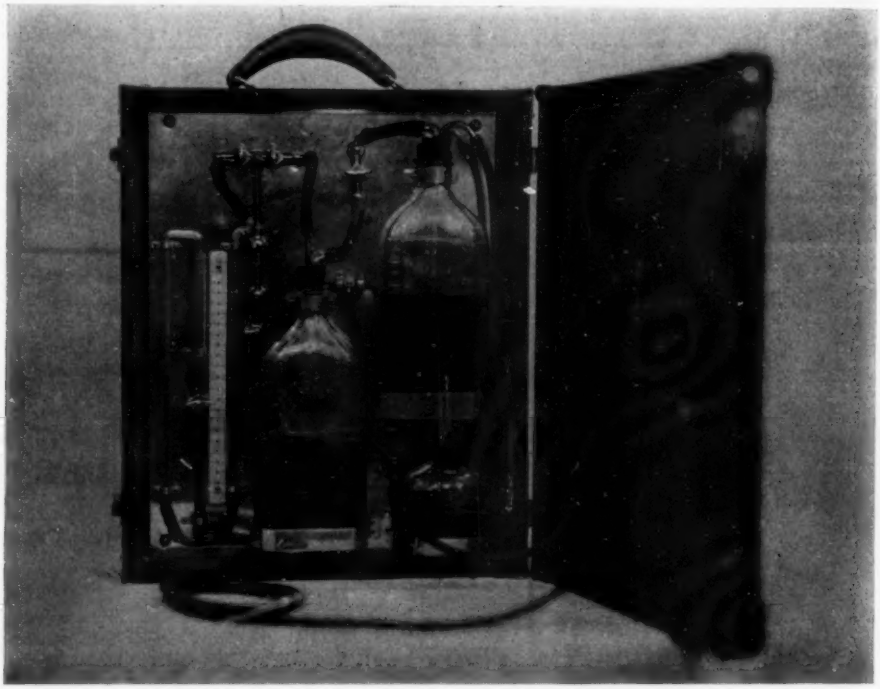

FIG. 1

The centrally situated water reservoir serves to collect any or all fluid forced from the open tube following a sudden rise of intrapleural pressure due to violent coughing, sneezing or straining by the patient. Spilling of manometer fluid, with consequent loss of time in refilling the tube, is minimized by this arrangement.

All working parts of this apparatus are fixed by means of aluminum strips or metal supports to an aluminum-covered wooden board $\frac{1}{4}$ inch thick. The instrument panel is enclosed in a leather carrying case, 17 inches long, 14 wide and 4 deep. The complete outfit weighs 15 pounds.

SUMMARY

1. The apparatus described is compact, easily portable, and especially adapted for use at the bedside.

2. A maximum displacement of 800 cc. of air is available through siphonage.

3. When extraordinary amounts of air are needed for collapse purposes, resiphonage may be accomplished without detaching the air-tube from the needle.

4. A device is provided for absorption of oxygen from atmospheric air, and the shunting of either air or nitrogen gas to the pleural space.

5. The inclusion of a receptacle intermediately in the path of the air-tube is a protective measure.

6. A manometer with a central water reservoir and stopcock ensures against accidental spilling of fluid, and may be filled and refilled with a minimum loss of time.

THE EFFECTS OF TUBERCULO-PROTEIN (MA-100) ON THE COURSE OF EXPERIMENTAL TUBERCULOSIS IN RABBITS AND GUINEA PIGS[1]

K. C. SMITHBURN, F. R. SABIN, AND J. T. GEIGER

A portion of the coöperative research sponsored by the National Tuberculosis Association has been devoted to the chemical analysis of tubercle bacilli and the subsequent testing of the biological properties of the various chemical fractions derived from tubercle bacilli. The bacilli have been grown upon protein-free media, and the fractions obtained from them have been tested first on normal and then on tuberculous animals, to determine whether their administration had any effect upon the course of the tuberculous infection.

The fact that tuberculo-protein MA-100, obtained from the media on which tubercle bacilli had been grown, can sensitize an animal, that is, give the Arthus phenomenon, while Old Tuberculin does not sensitize but still gives a positive reaction in the allergic state, provides an opportunity to study the relation of protein sensitization to resistance in tuberculosis.

The altered reactions of the body to a second tuberculous infection, first described by Koch (1), remain a fundamental problem of the disease. These changed reactions may be listed as follows:

The Koch Phenomenon: Koch showed that the second injection of living tubercle bacilli into the skin of guinea pigs was followed by reactions differing from those induced by the first; that the signs of a reaction appeared earlier, that an ulcer formed quicker, and that the lesion healed promptly, while that due to the first injection did not.

Increased Destruction of Bacilli: Rist, Léon-Kindberg, and Rolland (2) and Rist and Rolland (3) showed that there is an increased death of bacilli in the zone of a second inoculation. They found, both by the intraperitoneal and the subcutaneous route, that in the area of the second infection tubercle bacilli become fragmented and show a changed staining reaction with the Ziehl-Neelsen technique. Then they extirpated small pieces of the skin both after the first and the second inoculation, introduced them

[1] From the Laboratories of The Rockefeller Institute for Medical Research, New York.

under the skin of normal guinea pigs, and found less severe lesions from the material of the second injection. Krause and Willis (4) immunized guinea pigs with an avirulent strain of tubercle bacilli, R1, and then showed on reinjection, this time with virulent tubercle bacilli, that during the first two weeks after the latter living bacilli did not reach the regional lymph nodes in sufficient numbers to infect another animal, whereas after a first infection they could be found in the lymph nodes within an hour. Rich (5) was unable to distinguish differences in the numbers of bacilli at the site of injection during the first few days after first and second injections, but afterwards there were many more in the primary lesions. While it is admittedly difficult to determine the death-rate of the tubercle bacillus in the body, nevertheless all of these observations can be interpreted on the basis of an increased destruction of tubercle bacilli in the immune animal.

Accelerated Tubercle-Formation: Krause and Peters (6) found that a tubercle of epithelioid cells formed sooner in the zone of a second injection of tubercle bacilli under the skin than after the first. There is evidence to show that the epithelioid cell is produced by a phosphatide liberated from dead tubercle bacilli. In view of this fact, the phenomenon of accelerated tubercle-formation would be expected if there is an increased death of tubercle bacilli in the zone of the second injection.

Increased Resistance: On the basis of the Koch phenomenon, there has grown up the concept that increased resistance to tuberculosis is built up through an infection mild enough to be controlled. This is in accordance with the results of all of the studies of the natural infection in man, with the work of Calmette on vaccination with *BCG*, as well as with all of the experiments involving increased resistance to tuberculosis through vaccination with heat-killed bacilli (Petroff (7), Petroff, Branch and Jennings (8), Thomas (9), and many others), or with partially defatted tubercle bacilli (Dreyer (10) and Smithburn (11)).

Temperature Reaction: Increased sensitivity to tuberculin or to tuberculoprotein is shown by the temperature. The tuberculous animal shows a higher rise in temperature following an injection of tuberculoprotein than the normal animal given the same amount (12).

Skin Hypersensitivity: The tuberculous animal may give a positive reaction to the intracutaneous injection of tuberculin and tuberculoprotein. The factors involved in this reaction are unusually great permeability of blood-vascular or lymphatic capillary endothelium, or both, resulting in oedema; at times sufficient damage to vascular endothelium

to produce haemorrhage; an increased chemotactic effect on leucocytes; an increase in lymphocytes and monocytes in the tissues around the site of injection; and necrosis.

Anaphylaxis: As indicated by spasm of the smooth muscle of blood-vessels or bronchioles. From time to time, all of these changed reactions, which have been analyzed through the study of the Koch phenomenon, have been described under the term of allergy. It is obviously important to determine which phenomena included under this term are referable to protein sensitization and whether they have any relation to resistance.

PROCEDURES AND RESULTS

Eight rabbits and 9 guinea pigs received the tuberculoprotein and later were inoculated with virulent tubercle bacilli. Thirty control rabbits and 10 control guinea pigs were inoculated with virulent tubercle bacilli at the same time as those receiving the preliminary treatment with tuberculoprotein. The blood of each animal was studied before any experimental procedure. Haemoglobin estimations were made by the Newcomer method. Total erythrocyte and leucocyte counts, as well as differential leucocyte counts, were made, the latter by the supravital method. The studies of the blood were continued throughout the course of injections of tuberculoprotein, and after inoculation with tubercle bacilli. Analysis of blood studies revealed that the protein did not significantly influence any of the blood cells. Moreover, the "treated" animals after inoculation with tubercle bacilli showed no significant difference from the controls with regard to the blood cells.

Tuberculoprotein MA-100 was obtained through the courtesy of Dr. John Reichel, from the Mulford Laboratories, Sharp and Dohme, Glenolden, Pa. Dilutions were freshly prepared with sterile physiological saline solution once or twice weekly, according to the increase in amount given. For the rabbits the dilutions were prepared so that the desired amount of protein was in each instance contained in 1 cc.; for the guinea pigs in 0.15 cc. The daily dose for each guinea pig was 0.15 of the dose given to the rabbits (calculated according to relative weights). Except as indicated below, all injections of the protein were made subcutaneously in the inguinal or lower abdominal regions. Table 1 shows the amount of tuberculoprotein given each animal and the date of each injection (table 1).

As will be seen from table 1, the course of daily injections covered a period of thirteen weeks before inoculation with tubercle bacilli. The injections were continued for about three weeks after inoculation.

Seibert (13) has shown that repeated injections of tuberculoprotein in large doses may induce cutaneous hypersensitiveness in nontuberculous animals. In the present experiment the last injection of the tuberculo-

TABLE 1

Table 1 indicates the dates on which injections of tuberculoprotein were made and the dose given on each day to the rabbits and to the guinea pigs. The total amount of protein injected before and after inoculation is shown

MGM. PROTEIN TO RABBITS	DATES OF INJECTION	MGM. PROTEIN TO GUINEA PIGS
0.000000001	October 13, 14	0.00000000015
0.00000001	15, 16, 17	0.0000000015
0.0000001	19, 20, 21	0.000000015
0.000001	22, 23, 24	0.00000015
0.00001	26, 27, 28	0.0000015
0.0001	29, 30, 31	0.000015
0.001	November 2, 3, 4	0.00015
0.005	5, 6, 7	0.00075
0.01	9, 10, 11	0.0015
0.05	12, 13, 14	0.0075
0.1	16, 17, 18	0.015
0.2	19, 20, 21	0.030
0.3	23, 24, 25	0.045
0.4	26, 27, 28	0.060
0.5	30	0.075
0.5	December 1, 2	0.075
0.6	3, 4, 5	0.090
0.7	7, 8, 9, 10, 11, 12	0.105
0.8	14, 15, 16, 17, 18, 19	0.120
0.9	21, 22, 23, 24, 26	0.135
1.0	28, 29, 30, 31	0.15
1.0	January 1, 2	0.15
0.15	4, 5, 6, 7, 8, 9	0.15
0.15	11, 12*, 13, 14, 15, 16	0.15
0.15	18, 19, 20, 21, 22, 23	0.15
0.15	25, 26, 27, 28, 29, 30	0.15
TOTAL MGM. PROTEIN TO RABBITS	**DATES OF INJECTION**	**TOTAL MGM. PROTEIN TO GUINEA PIGS**
27.198	Mgm. protein before inoculation	5.099
2.4	Mgm. protein after inoculation	2.4
29.598	Mgm. protein total	7.499

* Day of inoculation.

protein *before inoculation* was made intracutaneously as a skin test in both the rabbits and guinea pigs. Upon examination twenty-four and forty-eight hours afterward, each test, both in rabbits and guinea pigs,

was definitely positive. No reaction proceeded to necrosis, but in each instance there was a distinct red, indurated wheal, measuring from 6 x 7 mm. up to 18 x 25 mm. in the rabbits, and from 7 x 10 mm. up to 16 x 23 mm. in the guinea pigs. The skin reactions were in general less marked in the guinea pigs at forty-eight than at twenty-four hours. In the rabbits, however, the reactions were in several instances more marked at forty-eight than at twenty-four hours. These results indicate that tuberculoprotein MA-100, like many other proteins, can produce cutaneous hypersensitiveness.

Sabin, Miller, Doan, and Wiseman (12) demonstrated that tuberculoprotein, given intraperitoneally in a dose of 0.001 mgm. or more, induced a rise in temperature in guinea pigs. Bickford (14) studied the effect of this protein introduced intrathecally. He observed in normal rabbits a temperature response similar to that described by Sabin, Miller, Doan,

TABLE 2

Table 2 shows the average temperatures of 10 guinea pigs before and at hourly intervals after injections of varying doses of tuberculoprotein

DATE	MGM. PROTEIN INJECTED	TEMPERATURE (°F.)					
		Before injection	After injection				
			1 hr.	2 hr.	3 hr.	4 hr.	5 hr.
November 11, 1931	0.0015	102.5	102.6	102.4	102.5	102.2	102.6
November 18, 1931	0.015	102.7	102.6	102.2	102.3	102.0	102.2
December 30, 1931	0.15	102.3	102.2	102.3	102.0	102.5	102.7

and Wiseman, but found that the animal, subjected to repeated injections of the same amount of the protein, became refractory and did not respond with fever. A larger quantity of tuberculoprotein subsequently did elicit a temperature response, however. In view of these observations, it was deemed advisable to determine whether or not the temperature reaction would be exhibited following a protracted period of injections of the protein in amounts at first insufficient to cause fever. Once weekly throughout the thirteen weeks prior to inoculation, and during the time of daily injections of tuberculoprotein, the temperature of each guinea pig was taken at frequent intervals during the day. First the rectal temperature was taken, then the protein was injected, after which temperatures were taken at approximately hourly intervals. Table 2 shows typical temperature changes observed (table 2). The temperatures recorded are the average for 10 animals. On no occasion was there a rise in tempera-

ture of the magnitude of 1 degree, even when the dose of protein had been increased to 0.15 mgm. The latter amount is 150 times the temperature-inducing dose observed previously (12). It appears, therefore, that the protracted period of daily injections of tuberculoprotein, first in infinitesimal doses which were then increased to many times the toxic dose, had so affected the animals that the larger doses did not induce a thermal response.

After the 8 rabbits and 9 guinea pigs had received daily injections of the tuberculoprotein for thirteen weeks, these animals and their controls, 30 rabbits and 10 guinea pigs, were inoculated with virulent tuber-

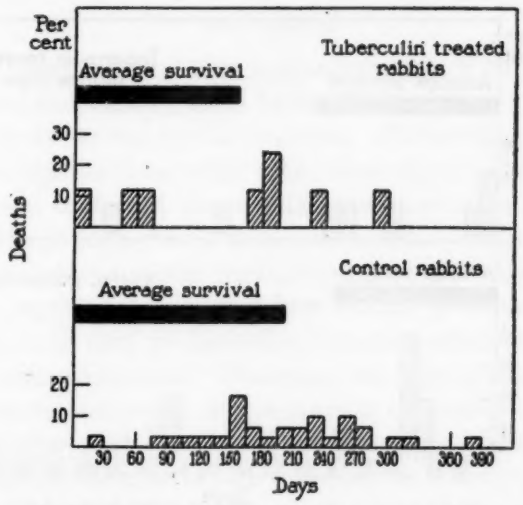

Chart 1. Shows the distribution of deaths of rabbits given tuberculoprotein and of their controls by 15-day intervals after inoculation with bovine tubercle bacilli. The average survival of each group is indicated in solid black.

cle bacilli. Each rabbit received intravenously 0.1 mgm. of a ten-day subculture of bovine tubercle bacilli, strain B1, in 0.5 cc. sterile saline solution. Each guinea pig received subcutaneously in the right groin 0.01 mgm. of a ten-day subculture of human tubercle bacilli, strain H37, in 1.0 cc. sterile saline solution. Each animal was allowed to succumb to the disease. The survival time of each was recorded and a careful study was made of the macroscopic and microscopic pathological changes.

The average survival of the 8 treated rabbits was 154 days, with 37.5 per cent of deaths occurring under 100 days (15). The average for the control rabbits was 201 days, with 6 per cent of deaths occurring under

100 days. This difference is probably not significant. Chart 1 shows the incidence of deaths among the rabbits by intervals of fifteen days, and the average survival of each group. The difference in average survival of the two groups of rabbits is perhaps less significant than the fact that in the treated animals a much higher percentage of deaths occurred in the acute phase of the disease.

The 9 treated guinea pigs survived an average of 172 days, with 44 per cent deaths under 100 days. The average survival of the 10 untreated control tuberculous guinea pigs was 154 days, with 60 per cent deaths in the first 100 days. This variation we believe to be not significant. The

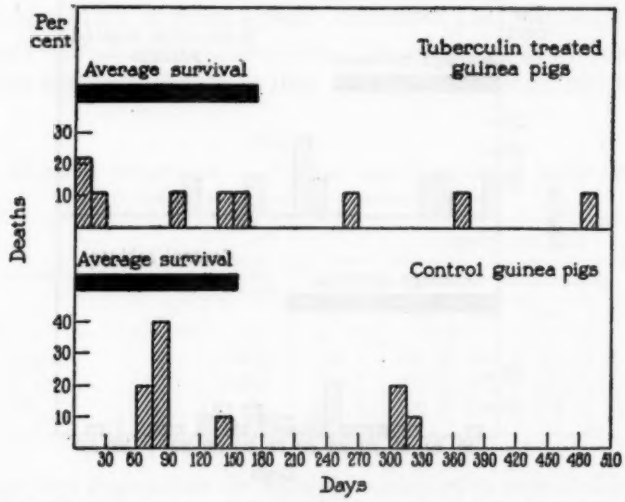

Chart 2. Shows the distribution of deaths of guinea pigs given tuberculoprotein and of their controls by 15-day intervals after inoculation with human tubercle bacilli. The average survival of each group is indicated in solid black.

incidence of deaths among the guinea pigs and their average survival are indicated on chart 2.

The rabbits receiving tuberculoprotein subcutaneously showed an average loss in weight of 130 gm. during the period of injections prior to inoculation. While we had no specific control series of rabbits on which weights were obtained during this period, we nevertheless believe this point may be significant since rabbits placed in the colony from stock almost invariably gain weight. From the time of inoculation until death, the animals receiving tuberculoprotein exhibited an average loss in weight of 800 gm., while their specific controls exhibited an average

loss of 652 gm. These figures were obtained by taking the difference between the last weight prior to inoculation and that at the time of autopsy and computing the average for the treated and control groups.

The surveys of macroscopic and microscopic pathological manifestations showed no striking difference between the treated and control rabbits, or between the treated and control guinea pigs. In the treated rabbits there was a greater incidence of lesions of the acute type ((15) (16)), but this may be explained entirely on the basis of a greater incidence of deaths in the early phase of the disease. Otherwise, no other effect on the tissue reaction, attributable to tuberculoprotein, was detected.

DISCUSSION

Seibert (13) demonstrated that tuberculoprotein, if obtained in a relatively pure and undenatured state, induced cutaneous hypersensitiveness as indicated by an Arthus type of reaction. She explained the failure of previous investigators to sensitize with tuberculins on the basis that the tuberculins used contained the original protein of the tubercle bacillus in a much altered form which possessed minimal antigenic properties. She also suggested that earlier workers had used too little of their tuberculins. The experiments reported here include a confirmation of Seibert's (13) work in that we have demonstrated cutaneous sensitization induced by tuberculoprotein. Moreover, we have studied the relation of induced hypersensitiveness to resistance in tuberculosis.

The concept that each reaction of the host to an invading pathogenic microorganism is of ultimate benefit to the host is one worthy of extensive examination. Most of the phenomena of tuberculosis now attributable to allergy, in the strictest sense in which that term can be used, have from time to time been associated with or made a part of immune reactions. There is growing evidence that allergy and immunity to tuberculosis may be largely unrelated phenomena. Willis's work (17) indicates that the natural wane of allergy accompanying healing lesions (R1 infection) is not accompanied by a decline of immunity. Similarly, the work of Rich (18) and his associates clearly demonstrates that one manifestation of allergy, namely cutaneous hypersensitiveness, may be abolished with little or no effect on the immunity. In one respect, the experiments reported here are the converse of those of Rich. That is, we have artificially induced cutaneous sensitization to the protein of tubercle bacilli without significantly affecting resistance. Thus we have another link in the chain of evidence which tends to dissociate allergy from immunity.

SUMMARY

Both rabbits and guinea pigs, subjected to a long series of daily injections of tuberculoprotein, became hypersensitive to this substance, as indicated by the intracutaneous reaction. Accompanying this induced hypersensitiveness, there was an abolition of the temperature response induced by the protein. Little or no effect on resistance to tuberculosis in either rabbits or guinea pigs was produced by the tuberculoprotein.

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THE SPONTANEOUS OCCURRENCE OF A NON-ACID-FAST FORM IN A CULTURE OF BCG[1]

STANLEY S. SIDENBERG AND E. E. ECKER

The problem of the variability of the tubercle bacillus is as old as the identification of the microörganism itself. As early as 1883 Malassez and Vignal (1) had observed non-acid-fast coccoid forms in zoogleic masses in skin lesions of a case of tuberculosis. In 1887 Ferran (2) noted changes in acid-fastness in cultures, and Auclair in 1903 reported similar findings. From that time on, numerous authors reported on the pleomorphism of the organism. Krylow (4) (1912) showed that tubercle bacilli were at first non-acid-fast and gram-negative, and only later acid-fast. Wherry (5) (1913) cultivated non-acid-fast coccoid, rod, and spore-like forms from a saprophytic strain of tubercle bacilli; eventually these forms regained their acid-fastness. Vandremer (6) (1931) affirmed that the tubercle bacillus is not obligatorily acid-fast. Maher (7) observed a non-acid-fast egg-shaped organism of the size of *B. subtilis* in a culture of the bovine blue strain. Kirchner (8) also noted non-acid-fast bacilli of the human and bovine types; all of these bacilli ultimately reverted to their acid-fast state. Pla y Armengol (9) reported "forms of the tubercle bacillus bio-pathogenetically similar to spores." In a careful and extensive study of single-cell cultures Kahn (10) presented conclusive evidence of the complex life-cycle of the tubercle bacillus, including a demonstration of non-acid-fast forms which later reverted to the acid-fast variety. Finally, Miller (11) (1932) succeeded in forcing 6 strains of *Mycobacteria* to grow as non-acid-fast organisms by adding a filtered extract of the chromogenic H37 strain of *B. tuberculosis* to the culture media.

A review of the literature from 1920 on, when reports on *BCG* first appeared, has disclosed only one paper (Feigin, Prokopowicz and Wierzbowski (12)) that demonstrated a variability (polymorphism) of the *BCG* organism. The variant forms were seen in faecal material from the newborn following vaccination with *BCG*. The cyanophilic elements increased in amount as more of the *BCG* was fed. While the variability of the tubercle bacillus had thus been demonstrated again and again,

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Calmette (13) in 1925 still stood firm in his assertion "that the *BCG* is always acid-fast and absolutely avirulent for animals. . . . It is a true Koch's bacillus but physiologically modified." As late as 1932 Calmette (14), though recognizing various forms of the tubercle bacillus, failed to acknowledge their presence in his *BCG* strain. Petroff (15), however, repeatedly insisted that the human and bovine bacilli are not absolutely distinguishable. He was consistent, therefore, when he wrote that the *BCG* is not a *bacillus fixé* in the sense of Calmette.

We now wish to report on a spontaneous variant observed in a culture of *BCG* obtained directly from the Pasteur Institute through the kindness of Professor Calmette.

EXPERIMENTAL

The *BCG* culture in a hermetically sealed Roux tube was received on February 2, 1932. The culture was grown in Calmette's bile-potato-glycerol medium and approximately 1 cc. of glycerol-bile covered the bottom of the tube. The potato slant was covered by a profuse, moist, cream-colored, smooth growth of individual colonies, approximately 3 mm. in diameter. The colonies were adherent at their borders. Smears of the original culture showed non-acid-fast rods, 4–8μ long and 1μ broad, with only an occasional acid-fast rod. The non-acid-fast rods gave the impression of sporulating organisms. This observation led to the heating of a fraction of the culture at 80°C. for 40 minutes in order to exclude the possibility of dealing with a spore-bearer. The heated suspension was then implanted in deep columns of boiled (cooled to 80°C.) calf-brain broth, after which the tubes were sealed with sterile vaseline. At the end of 21 days the tubes remained sterile. Similarly, ordinary media (plain agar, broth, etc.) failed to show any growth when aerobically incubated. The original *BCG* culture was then concentrated with 10 per cent H_2SO_4 according to the method of Loewenstein (inoculation must be made within 25 minutes of original concentration of organisms with H_2SO_4). The concentrate was transplanted to potato-bile-glycerol, Loewenstein's congo-red, and Lubenau's media. Unconcentrated material was also implanted on other tubes of the same media. After 10 days there was little evidence of growth in the unconcentrated transplants. Smears at that time showed a mixture of acid-fast and non-acid-fast bacilli. This in itself was of importance in that, if the culture were impure, the contaminants would have completely overgrown the *BCG*. This assumption is supported by the recent work of Woldrich and Singer (16).

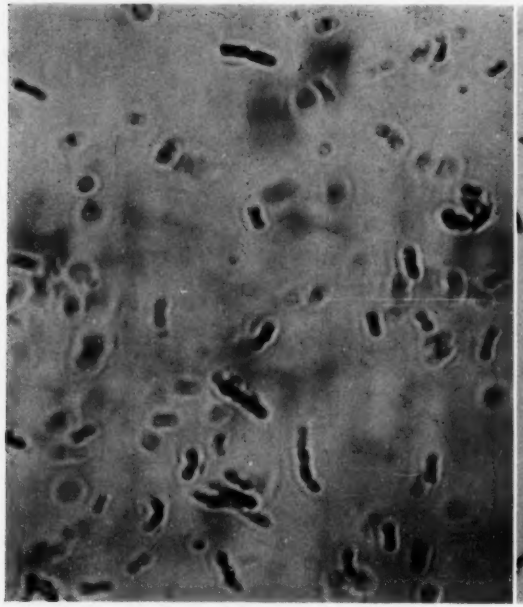

FIG. 1. ORIGINAL *BCG* CULTURE, CONTAINING NON-ACID-FAST FORMS

FIG. 2. TRANSITION OF NON-ACID-FAST TO ACID-FAST FORMS

FIG. 3. PRACTICALLY PURE CULTURE OF ACID-FAST RODS

The concentrated transplants eventually showed the same curious admixture of acid-fast rods with non-acid-fast forms. Transplants were then made of both the concentrated and unconcentrated cultures to Loewenstein's congo-red, Lubenau's, Sweaney-Evanoff's, Miraglia's potato-bile-glycerol and Petragnani's media as well as to Loewenstein's liquid media, the same media in which hydrocele fluid was substituted for human serum, and to Sauton's medium. It was hoped to obtain a pure culture of the non-acid-fast organisms, but these gradually disappeared, the acid-fast forms replacing the non-acid-fast type. After July, 1932, only the acid-fast type remained in the subsequent transplants. These acid-fast rods were 2 to 4μ in length and approximately 0.4μ in width. However, non-acid-fast forms were still observed in the original transplants. Both smooth and rough colonies noted on our solid media showed only acid-fast bacilli. On liquid media the growths were often filmy, often crepe-like, and again a combination of the two kinds. On solid media the colonies appeared as the typical *BCG* individual pinpoint colonies or as conglomerations of these colonies forming masses of about 1.5 mm. in diameter and 1 mm. in height. They also appeared as waxy, white to tan-colored colonies, resembling tapioca pearls. These colonies had a diameter of 1 to 2 mm. and an elevation of 0.75 mm. Their surfaces were smooth, even and moist. Their almost gelatinous character was in contrast to the dull, white, granular, moist, but not weeping colonies of the accepted *BCG*. The original culture received from Paris in February, 1932, was moist, so that lack of acid-fastness cannot be attributed to insufficient moisture. In all of our transplants we discovered only one obvious contaminant.

Since Smeeton and Rettger (17) clearly demonstrated that certain of the aerobic spore-forming organisms will, when cultivated on egg medium at 37°C., exhibit pleomorphism and varying degrees of acid-resistance characteristic of the streptothrices, the growths of *B. mycoides*, *B. megatherium*, and *B. mesentericus* were compared with our varying *BCG*. These aerobic spore-bearers grew readily in 24 hours on plain agar, while the *BCG* variant showed the characteristics of tubercle bacilli; namely, no growth on plain agar, slow growth on the accepted media for the growth of tubercle bacilli, typical colony form, etc.; so that it must be concluded that the variant in this *BCG* culture is not a contaminant of the type of these aerobic spore forms. Cultures of the variant that became acid-fast did not revert again to the non-acid-fast state.

The varying culture was then injected into a series of 10 guinea pigs,

each of which was negative to 0.1 mgm. of O.T. Five animals received the bacteria from solid media and five the bacteria from Sauton's medium. The organisms were suspended in saline solution and injected subcutaneously into the right groin. The results of these inoculations are seen in table 1.

It was noted that the injection nodules produced in guinea pigs that received large amounts of *BCG* became necrotic without any inflammatory reaction. Smears of the creamy, gelatinous and purulent discharge showed acid-fast rods and cellular débris. After the contents of the nodules had discharged the skin healed completely, so that no nodules

TABLE 1

*Showing the effects of inoculations of a varying form of the BCG organism into guinea pigs about 450 gm. in weight**

DATE OF INJECTION	NUMBER OF GUINEA PIGS	AMOUNT INJECTED	DATE OF DEATH OF ANIMAL	SMEARS FROM INJECTION NODULE	SMEARS OF		
					Inguinal node	Lung	Spleen
November		*mgm.*					
12	2,889	1.0	December 7	Negative	Negative	Negative	Negative
3	529	1.8	December 1	Negative	Negative	Negative	Negative
12	2,895	3.0	January 26	Negative	Negative	Negative	Negative
3	530	5.35	January 19	Negative	Negative	Negative	Negative
12	2,891	7.0	January 5	Negative	Negative	Negative	Negative
12	2,080	10.0	November 29	Negative	Negative	Negative	Negative
12	2,896	16.0	December 3	Positive	Positive	Negative	Negative
3	532	28.4	November 21	Positive	Positive	Negative	Negative
3	533	35.5	November 24	Negative	Negative	Negative	Negative
3	2,091	53.25	December 22	Negative	Negative	Negative	Negative

* All the organisms injected, November 3, were from growths on solid media, while those injected, November 12, were from growths in liquid media (Sauton).

were found in those animals living sufficiently long to allow for resorption. In some cases a few venous strands marked the site of injection; in others there were no signs whatever. Two guinea pigs showed more extensive reactions. Number 532, at autopsy, revealed a pseudotuberculosis of the bases of both lungs,—white elevated nodules, 1.5 mm. in diameter, were scattered throughout the bases. There were no grayish atelectatic areas so characteristic of early tuberculosis. Pus from the nodule at the site of injection yielded tubercle bacilli as did one of the inguinal lymph nodes. Smears of the lung, as well as of the spleen and of the liver, were negative. Similarly, guinea pig no. 2896 showed an injection nodule and inguinal lymph node in which acid-fast bacilli

could be demonstrated and recovered. Smears of the lung, spleen, and liver were again negative. Smears and sections from the other animals revealed no acid-fast bacilli.

CONCLUSIONS

1. A non-acid-fast variant of *BCG* was discovered in a culture obtained from Paris on February 4, 1932.

2. The variant possessed the growth properties of the tubercle bacillus and reverted to the acid-fast form when grown on various tubercle-bacillus media over a sufficient lapse of time.

3. The variant showed none of the characteristics of a contaminating organism.

4. Guinea-pig inoculations yielded cold abscesses at the site of injection. Acid-fast organisms were recovered from these abscesses.

5. Although the *BCG* is not a fixed form of microörganism and though it may yield a variant as described, the variant was devoid of pathogenicity for guinea pigs.

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CERTAIN ASPECTS OF PULMONARY TUBERCULOSIS IN CHILDREN

With Special Reference to Prognosis

ROY MORGAN[1]

The State Sanatorium at Westfield, Massachusetts, was opened March 1, 1910. Children have always been admitted, but since 1920 the institution has been devoted exclusively to children with pulmonary and hilum tuberculosis. From 1910 to the end of 1932, 631 cases of pulmonary tuberculosis of the adult type in children and adolescents (under eighteen years of age) have been under observation. The infrequency of this type of infection in the general population is indicated by the finding of only 203 such cases among 275,252 school children examined (1924–1932) during the course of the Chadwick Clinic in Massachusetts (1 to 1,300 children). In view of the scarcity of published data on this type of tuberculosis it seems desirable to review the experience at Westfield with special reference to prognosis and treatment.

The cases may be divided for purposes of discussion into three groups:

1: In the first group are 200 cases admitted from March 1, 1910, to March 1, 1920. These are placed in a separate group because no roentgen-ray apparatus was available during this period. The diagnosis was established in this group by the presence of tubercle bacilli in the sputum.

2: The second group comprises 195 cases admitted from March 1, 1920, to March 1, 1927. In these cases the diagnosis was made on the roentgen-ray findings, with or without positive sputum. All cases in this group reacted to the tuberculin test.

3: In the third group are 126 cases admitted from 1929 to 1930. The diagnosis in these cases was established as in the previous group.

In all groups only patients under eighteen years of age are included. Follow-up figures are based on reports secured in May and June 1932.

INFLUENCE OF AGE AND SEX

In table 1 the cases admitted from 1910 to 1927 are classified as to age and sex. Since there was no significant difference in age-distribution

[1] Westfield State Sanatorium, Westfield, Massachusetts.

between the two groups, the figures have been combined and so include all admissions from 1910 to 1927.

TABLE 1

Pulmonary tuberculosis in children admitted to Westfield Sanatorium 1910–1927
Age on admission

AGE	GIRLS	BOYS	TOTAL
4		1	1
5		4	4
6			
7	5	4	9
8	4	1	5
9		2	2
10	10	3	13
11	14	2	16
12	16	6	22
13	37	10	47
14	47	18	65
15	67	37	104
16	60	24	84
17	17	6	23
	277	118	395

These figures confirm the common experience that pulmonary tuberculosis is not a frequent disease in children before their teens. They also show the marked excess of females among children who develop pulmonary tuberculosis. This ratio is approximately the same as that for death-rates of males and females of the same age-groups for the corresponding period in Massachusetts.

IMPORTANCE OF CONTACT

Regarding the history of contact, there was no significant difference between the sexes or between the two periods we have studied. The combined figures (1910–1927) showed 176 cases with positive family histories, 185 with negative family histories, and 34 unknown or uncertain.

At present a great deal of attention is being paid by clinics to the examination of contact cases. This is a logical procedure. Among these, more tuberculosis will be found with a given amount of effort. At the same time we should realize that a large number of cases have no known contact and that every practical method of case-finding should be used.

MODE OF ONSET

As a rule, the mode of onset of pulmonary tuberculosis in children is almost impossible to determine. In fact our clinic experience in more recent years has shown that the disease in a large percentage of cases progresses for some time before any symptoms at all are noted. We have frequently observed this period of apparent latency for a year or longer. Any figures as to mode of onset are bound to be more or less inaccurate but we give in table 2 the mode of onset for the group of 1910–1920. It should be remembered that all cases in this group were frank clinical pulmonary tuberculosis with positive sputum and that the mode of onset means the first symptom noted by the patient or his family.

TABLE 2

Mode of onset (group 1910–1920)

	NUMBER OF CASES	PER CENT
Cough	108*	64
Weakness	23	14
Haemoptysis	8	5
No symptoms (discovered by routine examination)	7	4
Chest pain	6	4
"Influenza"	6	4
"Pneumonia"	3	2
Fever	2	1
Scattering	5	3

* Followed whooping-cough three times, measles three times, and scarlet fever once.

Table 2 calls for no particular comment except perhaps to note that 14 per cent of these cases began with weakness. The importance of weakness as the initial symptom of tuberculosis in adolescents is well enough known by specialists in tuberculosis. The family physician, however, should be impressed with the idea that tuberculosis should always be considered in such cases. This rule would be a great help in the discovery of early cases.

CLASSIFICATION ON ADMISSION

Table 3 gives the classification on admission. The last column gives the percentage of incipient cases. The number of incipient cases was naturally lower in the 1910–1920 series because only positive-sputum cases were included in that group.

In 1924 the State Health Department began a state-wide school clinic through which 276,808 children were examined up to June 1932. High-school students were not included, however, until September, 1929.

In the years 1927–1929 our percentage of incipient cases increased markedly and there has been a further increase since the high-schools have been included in the clinic. These figures are encouraging, as they would seem to indicate that we are making real headway in the discovery of early cases. This increase in incipient cases, along with improved treatment, should lead to the hope that the mortality of tuberculosis in the teens may be materially reduced.

In table 3, figures are given for the years 1927–1929 and 1929–1932 in order to bring out the increase in incipient cases admitted.

TABLE 3

Classification on admission according to sex

	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	PERCENTAGE OF INCIPIENTS
Boys				
1910–1920	6	14	46	9
1920–1927	9	13	30	17
1927–1929	17	14	14	38
1929–1932	21	15	7	49
Girls				
1910–1920	6	30	98	5
1920–1927	13	48	82	9
1927–1929	18	14	33	28
1929–1932	43	16	24	52

Since none of the group of 1910–1920 were X-rayed it is impossible to gauge accurately the amount of involvement. We have, however, checked the occurrence of râles on admission. Râles below the 4th rib with the apices clear were disregarded. Three records were missing, leaving 197 cases. Of these, 26 showed râles on the right only, 35 on the left only, 94 in both lungs and 42 showed no râles at all. The absence of râles in 42 out of 197 cases, all of which had positive sputum, is certainly high.

Table 4 gives a comparison of X-ray findings and râles in the group of 1920–1927.

TABLE 4

Involvement: group 1920–1927

	BOTH LUNGS	RIGHT LUNG ONLY	LEFT LUNG ONLY	NEITHER	TOTAL CASES
X-ray	132	41	22		195
Râles	38	56	32	69	195

In this group it is found that 69 out of 195 cases showed no râles. These figures, with our observations since 1927, have convinced us that the stethoscope is of little value in detecting early tuberculosis in children. It is also our impression that the same thing applies to a lesser extent in adults. Four or five years ago we analyzed the histories of 2,400 outpatients, most of whom were adults. In round numbers 400 of these were definitely positive by X-ray. Of these 400, 150 showed no râles and 80 were entirely negative on physical examination. Much has been written on this subject in recent years and the matter is well understood among specialists. It should, however, be a part of our tuberculosis campaign to impress this upon the family physician.

In the group of 1920–1927 (195 cases in all) there were 52 cases showing cavities. These were classified according to Pinner's classification as PI-15, PII-35, and PIII-1. This classification was made on the admission film. A certain number of progressive cases developed cavities after admission but these were not considered.

Many of these cases had apparently developed their cavities quite rapidly. Two of them had to their own knowledge been sick but one month before admission. Five had been sick two months, six for three months, four for four months: 46 of the 52 cavity cases had bilateral involvement.

PROGNOSIS

Tables 5 and 6 give the stage on admission, condition on discharge, and the follow-up on the group of 1910–1920. In this group, rest treatment was not closely followed. Patients were kept in bed only when having fever and were let up soon after the temperature became normal. None of them received compression therapy of any kind.

It is unfortunate that 33 of the cases (tables 5 and 6) could not be traced. We made use of death-reports in tracing these cases; so it is reasonable to presume that a fair number of the thirty-three are living. But whatever allowance is made for these untraced cases, the figures are

TABLE 5

Condition on discharge: group 1910–1920

STAGE ON ADMISSION	NUMBER OF ADMISSIONS	APPARENTLY ARRESTED	QUIESCENT	IMPROVED	UNIMPROVED	DIED	DURATION OF DISEASE (IN MONTHS) FROM ADMISSION TO DEATH IN CASES WHICH DIED IN SANATORIUM
Minimal	12	7	1	2	0	2	6–68
Moderately advanced	44	11	5	3	12	13*	6–29–15–24–29–12–70 6–20–17–10–17
Advanced	144	8	11	12	52	61	**
Total	200	26	17	17	64	76	

* One death from drowning.

** 8–3–9–8–3–2–2–3–12–28
2–7–6–30–1–60–2–4–21–9
23–2–13–17–1–1–2–30–16–18
10–7–11–2–6–3–9–11–7–28
2–16–30–18–6–5–27–10–23–2
9–24–4–2–2–17–5–10–33–3
11.

TABLE 6

Follow-up on patients discharged living: group 1910–1920

CONDITION ON DISCHARGE	NUMBER DISCHARGED	NOT TRACED	LIVING	DEAD	DURATION OF DISEASE (IN MONTHS) FROM ADMISSION TO DEATH IN CASES WHICH DIED AFTER LEAVING SANATORIUM
Apparently arrested	26	13	6	7	59–22–91–22 50–72–74
Quiescent	17	7	1	9	25–50–78–68–110–72 192–97–102–43
Improved	17	6	0	11*	26–20–15–27–77–20 3–27–3–36
Unimproved	64	7	0	57	**
Total	124	33	7	84	

* One died of cerebral haemorrhage.

** 10–9–14–8–27–3–6–30–20–2
30–18–1–12–40–45–3–13–24–13
81–15–8–84–8–11–1–72–17–9
5–10–12–7–11–6–3–72–1–19
5–10–11–36–24–12–8–26–23–16
10–4–3–4–5–7–23.

bad enough. We can at least say that, of 200 cases, 76 died in the sanatorium and 84 after leaving, a total of 160 deaths. All but two died of pulmonary tuberculosis. There was one death from drowning and one from cerebral haemorrhage. Only 7 of the 200 are known to be living: 6 of these were reported to be in good physical condition and 1 fair; while 2 of these had been classed as incipient, 1 as moderately advanced, and 4 as advanced. The six that are in good condition now were all discharged as apparently arrested. The case reported now as in fair condition was discharged as quiescent.

By the use of prolonged rest and compression therapy, these figures would probably be better. Still it should be remembered that all of these cases had positive sputum and that 144 of the 200 were classified as advanced on admission. This constitutes an unfavorable series no matter what treatment be used. These cases, with our subsequent experience, have convinced us that the only logical attack against adolescent tuberculosis lies in a vigorous case-finding campaign. These cases must be discovered earlier.

Our series of 1920–1927 included 195 cases. In these the diagnosis was made on the X-ray film and positive skin test. Doubtful cases were excluded; so it may be fairly stated these were all cases of pulmonary tuberculosis.

Tables 7, 8 and 9 give the results in these cases.

As noted before, the group of 1920–1927 included 52 cavity cases. These cavity cases were as a rule rapidly fatal: 45 of the 52 were reported dead by June, 1932, 4 were living and 3 were untraced. In the cases which died, the average duration of the disease from the first recognized symptoms to death was a little less than 28 months. This compares with an average duration of disease in all fatal cases of 34 months.

Four of the 52 cases were reported as living on June 1, 1932. All of them were girls. Two were living and well 8 years from date of admission; 1 was reported as "fair" 8½ years from admission; and 1 was reported as living but "not well" 6 years from admission.

In the group of 1920–1927 we used a little more rest treatment, and artificial pneumothorax was used in 5 of this group. Otherwise, treatment was essentially the same in this as in the former group. Since this group was selected on the basis of X-ray findings and positive skin tests, and only 125 of the 195 had positive sputum on admission, these cases were naturally more favorable than the group of 1910–1920. When we

consider, however, that 112 were advanced cases, 52 had cavities, and that 133 had bilateral involvement, it is not a series in which we could expect very good results.

TABLE 7

Classification on discharge: group 1920–1927

CLASSIFICATION ON ADMISSION	NUMBER OF CASES	STILL IN SANATORIUM	APPARENTLY ARRESTED	QUIESCENT	IMPROVED	UNIMPROVED	DIED	DURATION OF DISEASE (IN MONTHS) FROM ADMISSION TO DEATH IN CASES WHICH DIED IN SANATORIUM
Minimal	22	2	13	0	5	2	0	
Moderately advanced	61	1	19	1	12	16	12	3–47–25–20–38–24–17–5 10–24–24–10
Advanced	112	0	10	2	18	44	38	*
Total	195	3	42	3	35	62	50	

* 35–6–47–18–10–6–15–11–6–2–1–20
10–4–18–12–5–4–5–3–1–14–10–38
7–36–5–3–3–1–7–7–27–19–6–5
6–15.

TABLE 8

Follow-up group 1920–1927; arranged as to condition on discharge

CONDITION ON DISCHARGE	NUMBER DISCHARGED	NOT TRACED	LIVING AND WELL	LIVING: CONDITION POOR OR FAIR	DIED	DURATION OF DISEASE (IN MONTHS) FROM ADMISSION TO DEATH IN CASES DYING AFTER DISCHARGE
Apparently arrested	42	8	13	7	14*	24–56–30–115–35–106–31–25–69–45 99–46–100
Quiescent	3	1	1	1	0	
Improved	35	7	6	2	20	81–20–43–18–13–48–78–47–30–52–80–26 41–55–86–27–22–25–60–46
Unimproved	62	8	3	2	49	**
Total	142	24	23	12	83	

* One of these died of pneumonia.
** 13–33–10–42–85–19–10–34–15–8–45–10–23
6–13–34–28–13–36–11–9–26–6–10–22–53
6–33–9–31–12–3–4–6–16–10–45–7–13
54–48–3–4–35–3–10–33–21–20.

The figures in these tables speak for themselves and we shall call attention to only a few of them. It will be noted that 12 of the moderately advanced cases died in the sanatorium while none of the incipient cases died. However, 9 of the incipient have died since. This means

that, in 1932, 8 out of 22 incipients were known to be living, and 21 out of 61 moderately advanced cases. The end-results in the incipient and moderately-advanced cases seem therefore about the same, though the incipient did better for a time. This can probably be explained by the fact that we did not take these incipient cases seriously enough, and discharged them too early.

Our results in these cases of 1910–1927 were undeniably bad. Many cases, however, had very extensive involvement and a good outcome could hardly be expected. Even with artificial pneumothorax and

TABLE 9

Follow-up of group 1920–1927; arranged as to classification on admission

CLASSIFICATION ON ADMISSION	NUMBER DISCHARGED LIVING	NOT TRACED	LIVING AND WELL	LIVING: CONDITION FAIR	DEAD	DURATION OF DISEASE (IN MONTHS) FROM ADMISSION TO DEATH IN CASES DYING AFTER DISCHARGE
Minimal.....	20	5	3	3	9*	24–20–31–69–52–6–86–54 (Average duration 43 mo.)
Moderately advanced....	48	9	16	5	18	** (Average duration 44 mo.)
Advanced.....	74	10	4	4	56	*** (Average duration 22 mo.)
Total.....	142	24	23	12	83	

* 1 died of pneumonia.

** 56–13–30–115–43–25–10–80–13–36
33–55–99–6–16–10–48–100.

*** 81–33–10–42–85–19–10–34–35–106
18–15–8–45–13–48–78–23–6–13
45–47–30–34–28–26–41–11–9–26
6–10–22–53–9–31–12–3–4–49
27–22–25–60–46–45–7–13–3–4
35–3–10–33–21–20.

surgery as practised today, the results would probably not have been much better with these advanced cases as so many of them were bilateral.

TREATMENT

As noted previously, our patients in 1910 were not given bed treatment unless this was called for by fever or other symptoms. The use of rest treatment was gradually extended, however, and was being used more or less in all cases by 1927. Therefore, it might be claimed that our poor results were due to a lack of rest treatment. To test this, in 1927 we

adopted the rule of giving at least one year of bed treatment to all pulmonary cases, regardless of symptoms or stage of disease. It is obviously too early to give a detailed report of the results, but a few comments on these cases might be of some interest.

In the minimal cases the results have been very good,—at least temporarily. In a considerable number there has been complete clearing by X-ray and the patients are clinically well.

Forty-nine moderately advanced cases were admitted from June, 1927, to June, 1930: 11 died in the sanatorium, 18 were discharged as unimproved, 13 improved, 6 apparently arrested, and 1 remains in the sanatorium in good condition and almost ready for discharge. Some of these cases did remarkably well, but, taken as a whole, the mortality is high.

During the same period we admitted 62 advanced cases. These were discharged as: 27 dead, 14 unimproved, 15 improved, 2 apparently arrested, and 4 remaining under treatment.

So far as we can judge, at present this prolonged bed treatment has been very efficient in many of the minimal cases and in a few of the moderately advanced and advanced. Still the mortality in the moderately advanced and advanced cases remains very high.

For the past two years we have been using artificial pneumothorax in suitable cases. This offers hopes of improving our results but not to such an extent as to greatly change the mortality figures. Unfortunately, this treatment often cannot be used on account of bilateral involvement or adhesions.

CONCLUSIONS

Our experience has convinced us that moderately advanced and advanced pulmonary tuberculosis in children and adolescents is an extremely serious disease. The vast majority of these cases will be lost even if given prolonged bed treatment. Incipient cases seem to do very well under bed treatment. The logical procedure is to find tuberculosis while it is early and curable. Clinics should be more widely conducted in the schools with the routine use of the tuberculin test and X-ray. Special emphasis should be placed on the examination of all children known to have been exposed to the disease. The public should be educated to the necessity of prompt treatment for every child in whom a diagnosis of pulmonary tuberculosis has been established.

THE TRANSFORMATION OF ADIPOSE TISSUE FOLLOWING EXPERIMENTAL TUBERCULOSIS

GEORGE A. BAITSELL AND KARL E. MASON[1]

1. INTRODUCTION

In a previous publication (1930) a description was given of the process of intercellular fibrous-tissue formation occurring in the testis of the guinea pig following experimental tuberculosis. The results herewith presented are concerned with the histological changes which take place in the adipose tissue of the fat-body and which bring about an abundant and widespread formation of fibrous tissue. They are based upon histological materials from the same animals and certain of the microscopical preparations used in the previous communication.

The main problem in the present study, as well as in the previous one, was to determine the origin of the fibrous tissue which appears so abundantly in the infected tissues following experimental infection with tubercle bacilli. In this connection attention should be called to the statement in the previous publication (1930, p. 617) that

> it is a well-known fact in pathology that almost any alteration in the normal condition of the tissues causes more or less fibrosis. Fibrosis constitutes a typical defense-reaction of the tissues. It would seem that, fundamentally, the process of fibrosis in tissues following infection with tubercle bacilli constitutes a defense reaction,—an attempt to seal off the infected areas from the sterile tissues so that the disease will not spread.

Thus it is apparent that fibrosis might normally be expected to occur in any tissue of the body following infection, and the question as to whether the infected tissue is more or less closely related to normal fibrous tissue has no special significance. This fact is of interest in the present study because it has long been recognized that a close relationship exists between adipose tissue and fibrous connective tissue, both in the embryo and the adult, and that, in fact, the former is to be regarded as a special variety of connective tissue in which the embryonic-tissue cells have become modified for fat storage.

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The results from the present study,[2] as presented in detail below, show that the invasion of the adipose tissue is followed by rapid and striking histological changes. An abundant exudate appears in the intercellular areas which gradually increase in size so that the vesicular fat cells are separated by large areas filled with the intercellular exudate. It is evident that many of the fat cells disappear entirely. The exudate which at first appears to be almost homogeneous in its nature soon becomes fibrillated. The evidence further indicates clearly that elements of the exudate gradually become transformed into the dense fibrous tissue which is so prominent in the later stages. In a comparatively short time well-developed tubercles, infiltrated and enclosed by the newly-formed fibrous tissue, appear widely distributed throughout the infected tissues of the fat-body. The final result is an almost complete change in the histological structure of the infected tissue. On the whole it is apparent that the fibrosis occurring in adipose tissue following experimental tuberculosis presents essentially the same story as previously shown in infected testicular tissues.

The present study of the development of fibrous tissue in animals experimentally infected with tuberculosis was undertaken at the request of the Medical Research Committee of the National Tuberculosis Association, and the work has been aided by liberal grants from that organization. Grateful acknowledgment is made for the assistance which has been given during the course of the investigation.[3]

2. MATERIALS AND METHODS

As described previously (1930)

male guinea pigs of approximately equal weight were segregated in pairs. One animal from each pair was designated as the *reinfected animal*, and the other animal of each pair was designated as the *control animal*. The reinfected animal of each pair received two inoculations of tubercle bacilli. In the first, or sensitizing inoculation a saline suspension of tubercle bacilli of low virulence (R1 Saranac Laboratory) was given either as an intraperitoneal injection or as a subcutaneous injection in the region of the left axilla. In the intraperitoneal inoculation approximately five million bacilli were given, and in the subcutaneous inoculation approximately twenty-three million. The second inoculation was a direct injection, into the

[2] Preliminary reports of this investigation were presented at the 23rd annual meeting of the National Tuberculosis Association, 1927, and at the December, 1932, meeting of the American Society of Zoölogists.

[3] Dr. Marion B. Sherwood, who for two years was associated with these investigations as a technical assistant, had general charge of the handling and culturing of the tubercle bacilli, as well as the inoculating, observing, and autopsying of the experimental animals. It is a great pleasure to acknowledge the splendid assistance rendered.

tissues of one testis only, of a saline suspension containing approximately five million tubercle bacilli from a highly virulent strain.

The control animal of each pair received only the direct testicular inoculation. The latter was exactly the same as received by the reinfected animal, and was given at the same time.

The observations are based on a total of 49 animals, all of which were killed by chloroforming at various intervals, ranging from 2 days to 105 days after the tuberculous inoculation into the testis. As soon as possible after killing an animal, pieces of the infected testes and associated structures, carefully sectioned in various planes determined by the areas of infection, were placed in the preserving fluid for fixing and hardening. The uninfected testis of each animal was sectioned in corresponding planes and preserved for comparison.

The following preserving fluids were used: (1) Zenker's with 5 per cent glacial-acetic acid; (2) saturated solution of mercuric chloride with 5 per cent glacial-acetic acid; and (3) Allen's B15 mixture. Of these Allen's B15 fixing fluid has proved to be the most satisfactory for this work. However, specimens of tissue from each testis were usually placed in all of the fixing fluids. After the fixation, the usual routine histological methods were followed for paraffin-embedding, sectioning and mounting. Tissues were usually sectioned at 10 micra, but in a number of instances sectioning of tissues for special staining was performed at 7 and 8 micra.

The following stains have been used: (1) Delafield's haematoxylin with eosin or orange-G for counterstain; (2) iron-haematoxylin; (3) Mallory's connective-tissue stain, using the formula as given in Mallory and Wright's *Pathological Technique* (ed. 8, 1924); (4) Bielschowsky's silver-impregnation stain; and (5) Ziehl-Neelsen's stain for tubercle bacilli. Throughout the experiments, sectioned material from each testis was stained by several of these methods in order to get as clear a picture as possible of the changes that had taken place in the infected tissues.

3. STUDY OF THE MATERIAL

Lying anterior to, and closely associated with, the definitive testis of the guinea pig, as well as that of various other vertebrates, is a considerable area of fatty, or adipose, tissue which is commonly referred to as the fat-body.

The general arrangement of the testis and associated structures is presented in figure 1, which shows the condition of an infected testis as it appeared at the time of autopsy. Compared with the condition in a normal animal the general arrangement as here figured is, of course, the same, but the infected fat-body and epididymis are considerably enlarged. The spread of the infection is indicated in the figure by the presence of numerous elevated tubercles which are to be seen quite generally

scattered over the surface of the testis (centre) as well as extending into the epididymis (below) and into the fat body (above).

Our field of study in the present paper lies in the tissues of the fat-body, and we may now proceed to a consideration of the histological changes which take place in these fatty tissues following the direct testicular inoculation with the tubercle bacilli.

In figure 2 a section of normal adipose tissue of the fat-body is presented at a magnification of 200 diameters. This material was taken from the infected testis of a control animal which was killed two days

FIG. 1. Testis and associated structures of reinfected animal (GP 42) killed 49 days after testicular inoculation. Fat-body above: vas deferens to the right.

after receiving the testicular inoculation. It presents the typical, irregular, honeycombed appearance of adipose tissue as commonly seen in sectioned material, and no extended description or comment is necessary. It will be noted that the walls of the vesicles are very thin and that the latter, for the most part, are in close contact. Occasionally small intercellular areas with nuclei scattered here and there are to be noted.

The histological changes taking place in the infected fat-bodies during the next few days are rapid and decisive, with the result that the typical condition of the fatty tissue as observed in figure 2 is radically altered in appearance. Among the most apparent of these changes is an increase

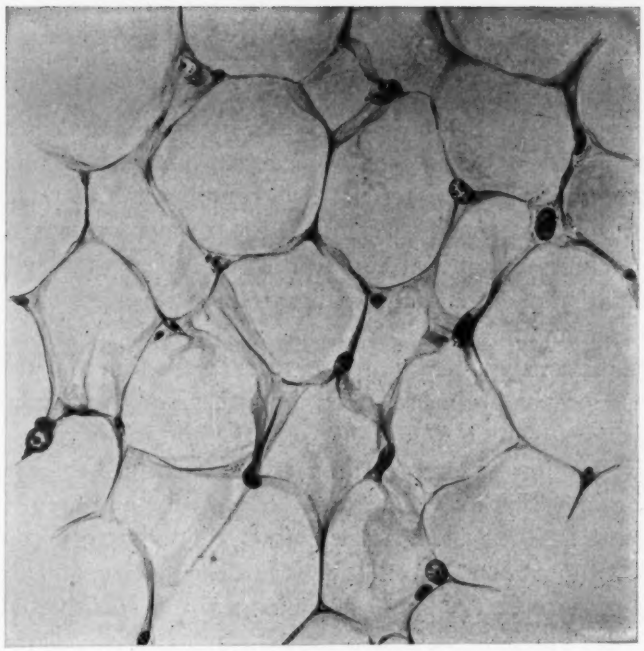

FIG. 2. Portion of normal adipose tissue taken from the uninfected testis of a two day control animal (GP 88). × 200.

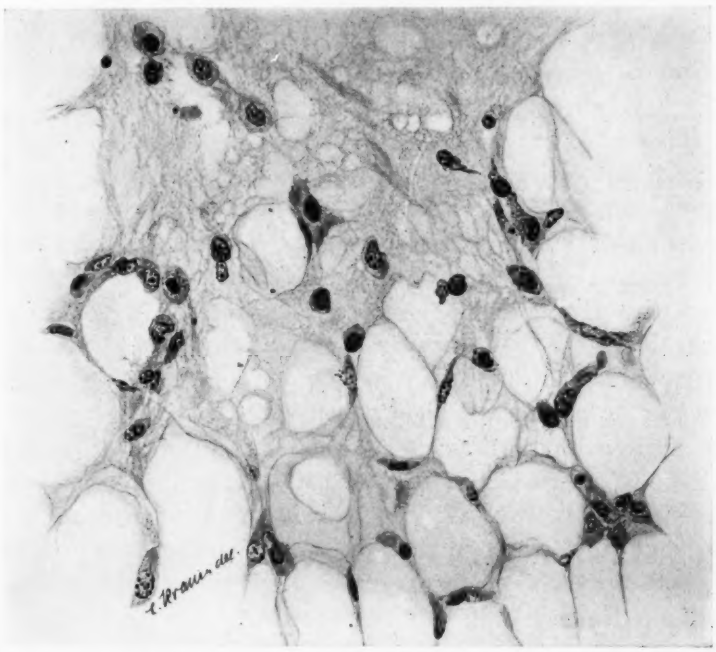

FIG. 3. Portion of an infected fat-body taken from a reinfected animal (GP 92) which was killed four days after the testicular inoculation. × 200

in the size of the intercellular areas and a corresponding decrease in the size of the fat vesicles, so that the latter become more or less separated by an abundant intercellular material. This condition is illustrated in figure 3, which was drawn from tissues infected four days previously. As the infection progresses many of the vesicles disappear entirely, resulting in the formation of large unbroken intercellular areas, as shown toward the top of the figure.

The preparations apparently give clear evidence that the transformation processes depend primarily upon the rather rapid accumulation of an intercellular exudate which is either secreted into the intercellular areas directly or else flows in from nearby regions. A further consideration of figure 3 makes this condition clear. Toward the bottom of the figure the adipose tissue still retains the normal condition to a considerable degree, but near the top the condition is just the reverse, and a large area of the newly-formed exudate has quite generally obliterated the fat vesicles. The exudate, as seen in such a preparation, shows marked fibrillation even at this early stage, but with a considerable degree of variation, which may range from extremely fine fibrillar elements, with every indication of being formed directly from the exudate, to much longer fibrils grouped more or less in parallel. Close study of this and similar preparations reveals no evidence of any direct cellular connection with the developing fibres,—the process appears to rest entirely upon an intercellular action.

The finer histological details of fibrosis, which results in the transformation of the adipose tissue, are portrayed in figure 4. It was drawn from a Mallory preparation at a magnification of 900 diameters. In the greatly enlarged intervesicular areas, here shown, the details of the fibrosis are revealed with extraordinary fidelity and clearness. In brief, it may be noted in this figure that the formed fibrillar elements vary in size from the very minute filaments loosely arranged in a delicate net-like grouping, as shown in the lower centre region of the figure, to a comparatively heavy bundle of wavy fibres, as shown, for example, in the lower left-hand corner of the figure. Intermediate stages occurring during the fibrillar formation, with respect to the two extremes just noted, are in evidence in various regions, but particularly in the upper right portion, where a grouping and fusion of the fine filaments are clearly evident, with a consequent formation of longer parallel fibrillar elements which tend to be arranged in bundles. The walls of the vesicles are breaking down, and the vesicular areas are invaded and obscured by fibrillar and cellular elements.

A more advanced condition in the fibrosis of the adipose tissue is presented in figure 5, which was drawn at a magnification of 400 diameters. The area here shown lies between two growing tubercles, an edge of each of which is indicated by the compact group of cells seen at the upper right- and the lower left-hand corners. The fibrous tissue lying between has been formed by a transformation of normal adipose tissue. Occasional obscure and hardly recognizable remnants of the fat vesicles are to be found. The extraordinary development and fibrosis of the intervesicular areas have been responsible for the almost complete disappearance of these storage cells.

In considering the mechanical factors concerned in fibrosis a comparison of figures 4 and 5 is of great importance, for in the latter figure we have the processes of consolidation and fusion of the first-formed fibrillar elements carried to a clear and definite conclusion. The evidence at hand from abundant material clearly indicates that the bundles of long wavy fibres have been formed as the result of a gradual union of the original minute fibrillar elements arising in the exudate. Furthermore, there is evidence that mechanical factors play an important part in the process. For example in figure 5, it appears evident that the finer fibrillar elements are being forced together by the continued increase in the size of the two tubercles as they more and more closely approach each other. The condition just noted is easily duplicated in the prepared material. The observations are in agreement that the fibrous tissue is heaviest and the bundles best formed in the region of transformed adipose tissue lying nearest to the growing tubercle, at which point the pressure from the increase in the size of the tubercle is presumably felt to the greatest degree. In agreement with this fact it will be noted that the fibrous tissue in the central region of figure 5, which lies directly in the path of the advancing tubercles, is much more advanced in its fibrosis than is the tissue in the upper left-hand corner of the figure which is somewhat beyond the effective growth-area of the two tubercles. To the right and left in this preparation, beyond the areas shown in this figure, the condition of the fibrous material approaches more and more closely to the condition shown previously in figure 4. An examination of figure 7, described below, in this connection is also very instructive. Here again it will be noted that the greatest concentration and development of the fibrous tissue are nearest to the advancing tubercle where the pressure is greatest.

In figures 4 and 5, then, it appears that the complete process of fibrosis of

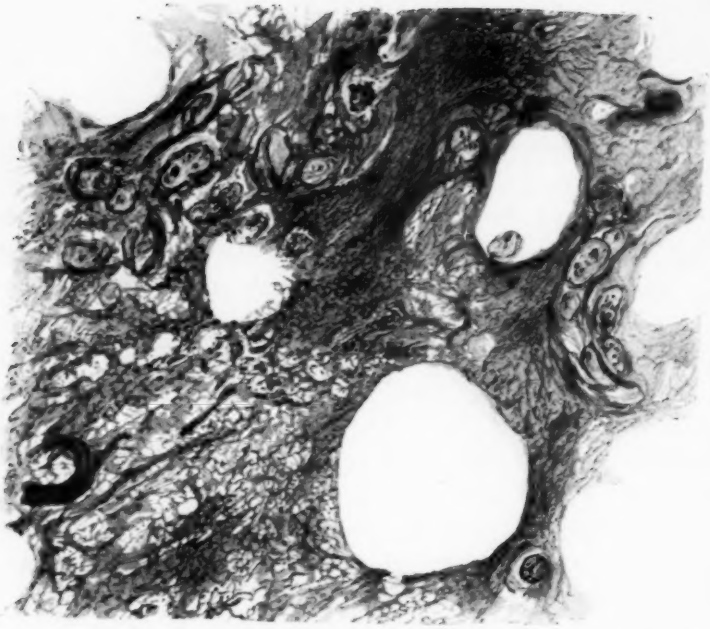

FIG. 4. Portion of the infected tissue from the fat-body of a control animal (GP 69), which was killed 18 days after testicular inoculation. × 900. Mallory stain.

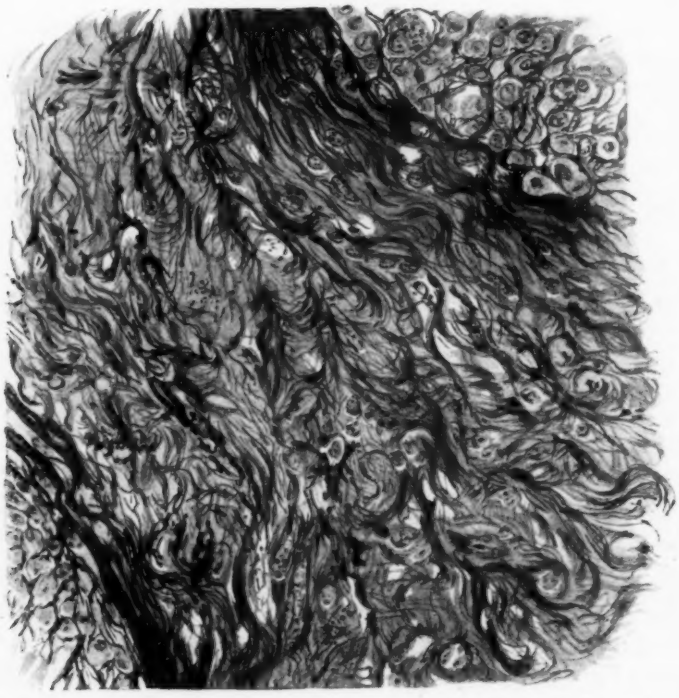

FIG. 5. Portion of an infected fat-body from control animal (GP 77) which was killed 20 days after testicular inoculation. × 400. Mallory stain.

the adipose tissue, considered from the structural standpoint, is indicated, beginning with the newly-formed minute elements in the exudate and continuing to the fully formed bundles of long, wavy collagenous fibres; the formation of the latter being influenced to a marked degree by mechanical factors.

The formation of the tubercle in the infected adipose tissue: As has been shown in the previous discussion, the transformation of the adipose tissue with the accompanying fibrosis begins shortly after the invasion of the tissue by the tubercle bacilli. Primarily it is clear that fibrosis is independent of the tubercle-formation which usually begins considerably later. It has also been pointed out (*cf.* figure 5) that the increase in the size of the tubercles may have, purely as a result of the mechanical factors involved, a marked effect upon the character of the adjoining fibrous tissue. This fact is shown in figure 6, which illustrates an early stage of tubercle-formation in the adipose tissue taken from the fat-body of a 21-day control animal. Other regions from this same preparation showing later stages in the tubercle-formation are to be seen in figure 7, which was stained with the Bielschowsky silver-impregnation stain in order to accentuate the fibrous-tissue formation. It will be noted in figure 6 that tubercles are forming in an area in which the fibrosis is already well advanced. Thus from the very early stages they are enclosed by layers of heavy fibres. It is evident from this condition that the fibrosis is independent of direct action by the cells composing the tubercles.

We may next consider a typical case in which the tubercle-development and associated fibrosis is essentially completed, such as is shown in figure 7. This preparation is from the infected testis of a control animal preserved 21 days after testicular infection and it was stained, as noted above, with Bielschowsky. The figure was drawn under low-power, and presents a section through a large tubercle, which may be seen to consist of several compact cellular groups more or less separated from each other by numerous strands of the infiltrating fibrous tissue. The entire tubercle is enclosed by a prominent band of fibrous tissue varying somewhat in thickness in different regions, but always composed of individual bundles of wavy fibres. In the region of the tubercle very little histological evidence remains of the adipose tissue, which shortly before occupied this area. In the peripheral regions of the figure, outside the tubercle, the transformation of the adipose tissue is somewhat less complete, and a considerable number of fat vesicles are in evidence.

Finally, we have shown in figure 8 another region from the same prep-

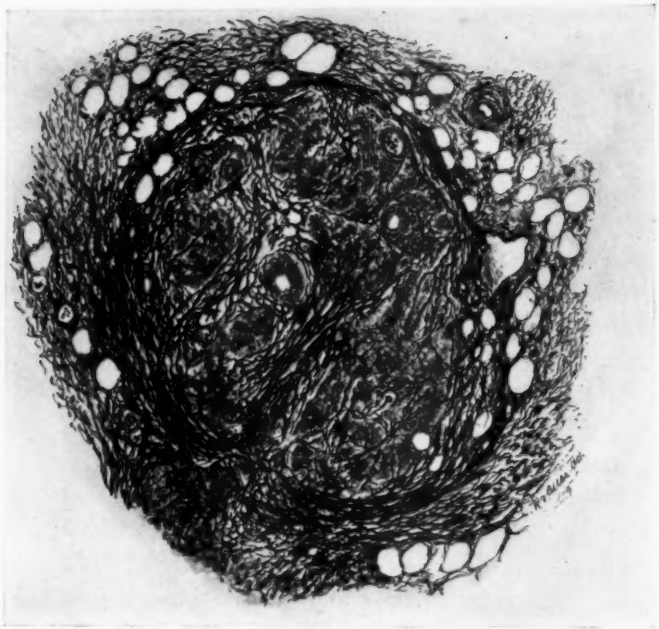

FIG. 7

FIG. 6

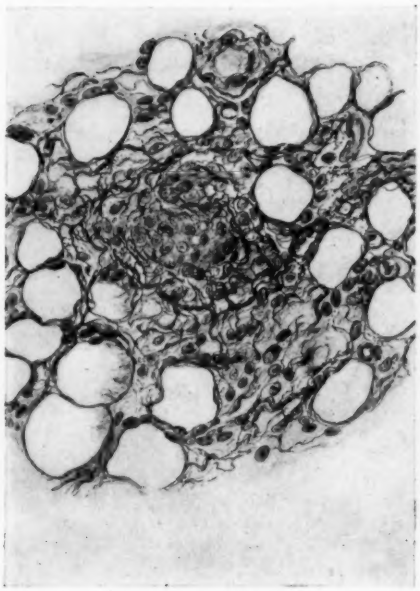

FIG. 8

FIG. 6. Portion of the infected tissue from the fat-body of a control animal (GP 64) which was killed 21 days after testicular inoculation. × 100. Mallory stain.

FIG. 7. Material from same animal as in fig. 6. Bielschowsky stain. × 100.

FIG. 8. Portion of the preparation shown in fig. 7. × 200

aration as figure 7 but at a higher magnification. Possibly it gives an even more striking illustration as to the extent of fibrosis which may take place in these tissues. In this connection it may be of value to compare the condition shown in figure 8 with the normal condition of the adipose tissue from this region, as previously shown in figure 2.

4. DISCUSSION

The results, as presented in the preceding pages, show that the invasion of the fat-body by tubercle bacilli causes a gradual breakdown and disappearance of the adipose tissue, together with the formation *in situ* of fibrous tissue. The fibrillar elements of the latter do not arise by the transformation of the structural elements of the fatty tissue, but by the gradual transformation of an abundant intercellular exudate which soon makes its appearance in the infected regions. The basic details of this process of fibrosis in adipose tissue appear to be exactly comparable to those taking place in fibrosis in the intertubular areas of the guinea-pig testis as previously shown (1930). And, furthermore, the formation of fibrous tissue in the tissues of the adult guinea pig following experimental tuberculosis occurs through the operation of the same methods, so far as we are able to observe, as obtains in the healing of wounds in adult frog skin (1916), in tissue-cultures of various frog-tissues (1915), or in the embryonic development of the fibrous tissues in the vertebrate embryos (1921, 1925).

Thus the evidence obtained to date from these various studies indicates that an essentially uniform method is responsible for the formation of fibrous tissue in the vertebrate organism under the varying conditions noted above. Fibrous-tissue development depends upon the formation of the definite fibrillar elements by a direct transformation of intercellular material. In the embryos of the frog and chick the intercellular ground substance arises early in embryonic development as a cellular secretion, which, in general, fills the spaces between the ectoderm and endoderm and into which the mesoderm cells later migrate. In the experiments with the cultivation of frog-tissues *in vitro* and in wound-healing in the skin of adult frogs, fibrosis was shown to be dependent upon a direct transformation of the fibrin elements of the blood plasma. Finally, following experimental tuberculosis in the adult guinea pig we find that a very heavy fibrosis occurs in the testis and in the fat-body by the direct transformation of an abundant intercellular exudate. The results obtained from these studies appear to warrant the following conclusions:

1: The fibrillar elements in the various types of fibrous tissue studied have their origin in an intercellular ground substance, which arises, directly or indirectly, as a cell secretion. No evidence has been obtained from the various studies, extending over many years and involving thousands of microscopic preparations, of fibre-formation occurring within the regular cell cytoplasm nor of its occurrence in a specialized outer, or exoplasmic, layer of cytoplasm. In 1915 when the first of these studies appeared, the Hansen-Mall exoplasmic theory of fibrillar formation was quite generally accepted. This was due to the generally recognized inadequacy of the rigid intracellular theory, as held by the Flemming school, to account for many firmly established facts regarding fibrillar formation in connective tissues. Increasingly within the last few years the consensus of histological opinion has swung still further from the intracellular viewpoint, including the exoplasmic modification, until at the present time the purely intercellular theory is generally accepted. The results of the present series of studies, together with the confirming results obtained during recent years by many investigators, such as Nageotte, Harrison, Huzella, Maximow, Bloom, Levi, Doljanski and Roulet and others, leave little doubt on this phase of the question, although in fairness it should be said that such able investigators as Laguesse, Studnicka, and Wassermann find in their results evidence for the exoplasmic theory. It seems evident that the negative results of Bofill-Deulofeu (1932) make no contribution to the problem.

2: The beginning of fibrillar formation in the various types of intercellular ground substance studied lies in the formation of definite, but minute, elements as the result of a coagulation and precipitation process, which from the structural standpoint, at least, appears to be identical with the process of fibrin-formation in blood-plasma. In some cases, as, for example, in the experiments with fibre-formation in the plasma clot (1917) and in wound-healing (1916), the structural basis of the fibres is known to lie in the fibrin filaments. It is, of course, recognized that fibrin is chemically different from the collagenous connective-tissue fibres, even though the transformed fibrin filaments appear identical from the structural standpoint. It has long been recognized, however, that old fibrinous deposits (Mall, 1896) react differently and appear to be chemically changed from freshly formed fibrin. Since we know that typical fibres, from the structural standpoint, may be formed by the direct transformation of the fibrin elements of the clot and, since it appears clear that they remain as the permanent fibres, it seems evident that they, as indicated by the staining reactions, gradually undergo a chemical transformation.

Maximow, Bloom, Momigliano-Levi, and others agree that the fibres arise in tissue cells by a precipitation process in the culture medium, here acting as a ground substance, but find no relationship between this process and fibrin-formation. They hold, in general, that the fibres originally appear in the

ground substance only in close proximity to migrating fibroblasts and as a direct result of a specific cell secretion. In support of the view that there is no relationship between the newly formed intercellular fibres and the fibrin filaments, Momigliano-Levi (1932) shows that fibre-formation will occur in a tissue-culture medium composed largely of blood-serum in which no fibrin is present. A condition of this kind, however, does not preclude the possibility that fibrin may be utilized when present. Thus, as shown in the frog and chick embryos, a fibrillar-forming ground substance is secreted very early and previous to any blood-supply. On the other hand, in cases involving connective-tissue formation in the adult, under normal or pathological conditions, the evidence is that the fibrin filaments formed in the exudate are utilized in the fibre-formation.

3: The minute, independent, fibrillar elements as originally precipitated from the ground substance are gradually orientated and consolidated through the influence of various mechanical factors. The structural details of this process can be illustrated in the plasma clot (1917) by the introduction of various mechanical factors, such as tension and pressure, which bring about a fusion and consolidation of the independent fibrillar elements and their definite orientation along lines of stress.

4: Finally, consideration may be given to the major rôles assumed by the cellular elements in the formation of fibrous tissue. In the first place they form the ground substance, in which the fibres later appear, as a secretion. In the embryo the ground substance is formed specifically for the connective-tissue development. In the adult the ground substance in which the fibres arise appears in many cases to be secreted as blood-plasma or as a tissue exudate and later utilized in the connective-tissue formation if the necessity arises. It is apparent from this situation that a close relationship exists throughout life between the common ground substance, the contained fibrillar elements, and the potential ground substance in the liquid elements of the blood and tissues. Undoubtedly the normal processes of repair or that occasioned by injury is attended to by coagulative and precipitative phenomena in the ubiquitous secreted blood and tissue fluids under the influence of the proper cell-groups.

This brings us to a consideration of the importance of the various types of connective cells in bringing about a modification of the common ground substance by their secretion of a substance specific for a particular type of fibrillar formation. Examples of this cellular action have been observed by Harrison (1925) in the formation of the basement-membrane in the amphibian balancer, by Maximow (1929), and by Momigliano-Levi (1932) in the formation of fibres in the culture media of tissue-cultures. Finally, the cells exert a powerful influence on the nature of the fibrillar formation through the influence of me-

chanical factors. Weiss (1933) has recently considered in excellent fashion the influence exerted by the "ultrastructures" of the ground substance on various developmental processes, by which the ultramicroscopic rods of the colloids are orientated in the embryo in accordance with a primary polarity or orientating force in the organism, and the cells in their migratory movements are believed to be influenced by the basic orientation of the micellae. In addition, however, it seems clear that there is a reciprocal action by the cells, due to tension and pressure produced as they move through the ground substance, and this results in a consolidation of the ultramicroscopic units to form the definite fibres. This is particularly evident in the case of cells in a tissue-culture migrating from the embedded tissue into the peripheral regions, and also in the pressure produced by the continued growth of a group of cells as shown in the tubercle-development in the present paper (p. 593).

SUMMARY

1. Adipose tissue from the fat-body of the guinea-pig testis, experimentally infected with tubercle bacilli, undergoes rapid and striking histological changes characterized by the formation of an abundant intercellular exudate. The normal vesicular fat cells in the infected region disappear for the most part and a dense fibrous tissue arises by a direct and gradual transformation of the minute structural elements of the exudate. After a time, cells grouped to form tubercles appear and as they enlarge are infiltrated and encapsulated by heavy bands of the newly-formed fibrous tissue. The development of fibrous tissue in infected areas of adipose tissue follows the same method as in infected areas of testicular tissues.

2. In the discussion it is pointed out that the results obtained recently by various investigators working on the development of various types of connective tissues, both embryonic and adult, strengthen the now generally accepted belief that the fibrillar elements have their origin in a purely intercellular material formed as a cell-secretion. It is also clearly indicated that a process involving the coagulation and precipitation of the intercellular material, influenced by further cell-secretions and by various mechanical factors, is responsible for the actual fibre-formation. The present results support the view, as stated in 1915, that fibre-formation in the mature vertebrate is directly connected with fibrin-formation in the blood-plasma.

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THERAPEUTIC PNEUMOPERITONEUM[1]

A Review of 100 Cases

ANDREW L. BANYAI

It is not our purpose to present an evaluation of the different methods of treatment of intestinal tuberculosis. The surgical as well as the conservative measures have their limitations, indications and contraindications. The only appropriate approach to this problem is the arrangement of treatment on the basis of the type and extent of the intestinal involvement and with due consideration of the factors which indicate the patient's general resistance, immunity, and the severity of other tuberculous lesions.

The symptomatic and curative value of treatment by induction of pneumoperitoneum, as found in a group of 44 patients, was reported in a previous publication (1). All but one of those patients had far-advanced pulmonary tuberculosis. The statistics of competent observers show that while the therapeutic results from surgery for intestinal tuberculosis might be quite satisfactory in patients with moderate, retrogressive or stationary fibrosing pulmonary tuberculosis, the probabilities for an improvement in advanced exudative lesions of the lungs are slight, if any. It can be seen that the patients comprising our first series could not have been recommended for surgery. The advanced pulmonary disease together with the toxic condition of those patients excluded them from natural or artificial heliotherapy.

Medicinal treatment was tried in every patient of that group, without appreciable benefit. Relying on the available sporadic reports concerning the usefulness of pneumoperitoneum treatment, this method was used in 100 cases at Muirdale Sanatorium. The therapeutic results in our first group (44 cases) can be summarized as follows: (1) symptomatic relief in 70.4 per cent; (2) complete relief in 31.8 per cent, partial relief from all intestinal symptoms in 22.7 per cent, cessation of diarrhoea while other symptoms persisted in 11.3 per cent, and persistence of diarrhoea while other symptoms ceased in 4.7 per cent.

In many instances early death prevented prolonged observation; still,

[1] From Muirdale Sanatorium, Wauwatosa, Wisconsin.

the symptomatic relief was often so striking that a more extensive use has been carried out since that time.

TECHNIQUE

In the absence of ascites, paracentesis of the abdominal wall is regarded with more or less reticence by medical men even though they have extensive experience with artificial pneumothorax. The reason for this lies not so much in the knowledge of possible disagreeable incidents, (because the number of these is extremely small), but (1) in the fear of puncturing the intestine and (2) in the lack of an accurate indicator which would register the entrance of the point of the needle into the abdominal cavity. It has been found by those using pneumoperitoneum for diagnostic purposes and also by clinicians who have been injecting blood into the peritoneal cavities of children that the probability of puncturing an intestine is practically nil. It does not occur, as a rule, when proper technique is followed.

When the needle reaches the abdominal cavity and is *slowly* forced inward, the omentum and the intestines being soft, pliable and movable, are pushed in front of the needle but are not punctured. We had the opportunity to observe often that, after the perforation of the abdominal wall with a large Floyd-Robinson needle, it slides deeper into the abdomen by the force of gravity, not infrequently, until the handle of the needle rests on the skin, without any harm being done to the abdominal organs. There are three things to be remembered in this connection: (1) the needle must be inserted slowly; (2) it must be pushed through the abdominal wall obliquely, and thus will increase the distance the needle has to travel and also the resistance of the tissues through which it passes, which automatically decrease the speed of the manoeuvre and thus avoids injury to the abdominal contents; and (3) while the needle is forced through the layers of the abdominal wall, it must be held back by a firm grip to avoid a sudden penetration and intestinal puncture.

When repeated inflations are carried out, there may be considerable scar-tissue formation at the site of previous punctures. Particular care must be exerted in such cases when one is introducing the needle through these more resistant fibrous areas of the abdominal wall.

The site of injection has been three fingers' breadth below and laterally to the umbilicus. Some prefer McBurney's point or the middle line at a point from one to three fingers' breadth below the umbilicus. In all these instances the evacuation of the bladder immediately before in-

flation is essential to avoid its possible puncture. Because of the thickness of the abdominal wall in one of our patients we were obliged to abandon the injection of oxygen in the left lower abdominal quadrant after several unsuccessful attempts were made. In this case the injection was tried at the subdiaphragmatic region on the right side. The advantages observed at that time made us resort to the same technique on successive occasions, and finally it has been adopted as the standard procedure for intraäbdominal oxygen injections.

Incidentally, abdominal paracentesis was also performed at the left-hypochondriac region. This case will be discussed in a separate section, because of its interesting aspects.

Local anaesthesia should precede every injection regardless of its site. The careful infiltration of the peritoneum is of utmost importance. We use 5 cc. of a 1 per cent solution of novocain. By elevating a skin fold between thumb and index finger a small skin incision is made to aid the smooth insertion of the needle.

For the subumbilical injection the Floyd-Robinson needle was used in all our cases. Its handle-like head ensures a firm grasp and easy handling. Its obturator prevents its being obstructed by blood clots or tissue particles. The obturator is withdrawn as soon as the point of the needle enters the abdominal cavity. The first bottle (the one next to the manometer) of the pneumothorax apparatus is filled with oxygen. If the needle is pushed only gently and it is passing through the tissues gradually, one can feel the resistance offered by the different layers of the abdominal wall. It happens sometimes that the inserted needle will glide on the anterior or posterior sheet of the rectus muscle or on the peritoneum. Such an occurrence might give the wrong impression that the needle reached the peritoneal cavity. It should be slightly withdrawn and then pushed through the tissues with enough force to prevent gliding. If the point of the needle did not reach into the abdominal cavity, but is lying in the tissues, the flow of oxygen will be very slow if inflation is attempted, and the manometer reading following 30 or 50 cc. of oxygen injection will show a nonoscillating, high, (+4, +6) positive pressure. As a matter of routine, the needle is connected with the pneumothorax apparatus, before it is inserted into the tissues.

OBSERVATIONS

One cannot rely on the manometer, as in the case of artificial pneumothorax, when the subumbilical area is selected for injection. The intraperitoneal pressure is *neutral* in this part of the abdomen; therefore, the

manometer will not show oscillations when the point of the needle enters the abdominal cavity. All our manometer readings were taken while the patient was lying on his back and during quiet respiration. Observations made with the patient in the Fowler and Trendelenburg positions revealed no change in the intraperitoneal pressure. No deviation from the neutral pressure was seen on repeated deep inspiration and expiration.

Hitzenberger (2) observed that the intraäbdominal pressure is increased on inspiration. The increased intraäbodminal pressure will increase the amount of blood in the lower extremities and, if the body is balanced on a board, it sinks down at the foot end on inspiration. However, the variations in the intraäbdominal pressure measured below the umbilicus are ordinarily so slight that they are not registered on the water manometer of the Floyd-Robinson pneumothorax apparatus. Suermondt (3) states that the normal intraperitoneal pressure (between the visceral and parietal peritoneum) is about atmospheric. There are some conflicting reports concerning the intraäbdominal pressure. Thus Wagoner (4) found it to be always negative, while Coffey (5) describes it as being always positive. The opinion expressed by Livingston (6) is fully corroborated by our clinical studies. He says that "within the abdomen no marked and generalized negativity is possible, for the abdominal walls are muscular and contain no bony frame work capable of resisting the force of the atmosphere. Normally, the general pressure within the abdomen must tend to equal rather than to be above or below that of the atmosphere."

Following the injection of certain amounts of oxygen it was found that the intraperitoneal pressure will rise in a certain number of cases. Out of 44 cases comprising our first group, positive pressure was seen only once following the injection of 300 cc. of oxygen. The registration of positive pressures is more frequent with larger quantities of oxygen. However, the rise is not always proportionate with the quantity of gas injected. The bodily response to these injections varies not only in different individuals but also from time to time in the same individual. This fact is well illustrated in table 1.

There are several factors which have a bearing on the intraäbdominal pressure: (1) muscular tonicity of the abdominal wall, as, for instance, the increase in pressure during defaecation and in the second stage of labor; (2) intravisceral pressure (stomach, intestines, bladder); (3) the presence of ascites or large abdominal tumors; (4) tonicity and integrity of the diaphragm,—it was found by Rasumov (7) that the tonicity of the

TABLE 1

Variations in the intraperitoneal pressure following oxygen injections in the first group of patients

SERIAL NUMBER	AMOUNT OF OXYGEN IN CUBIC CENTIMETRES																			
	150	200	300	400	450	500	550	600	650	700	750	800	850	900	950	1000	1050	1200	1300	1400	1500
1				0								+3									
2		0						0 0				0 0									
3													0								
4					0								0								
5												0 +1	+3	0		+1 0		0			
6										0											
7										+1		0									
8												0 +2				0		0			
9												+1 +2				0 +2					
10												0									
11						0															
12																0					
13								+8										0		+3	
14																+3 +3					
15																+2 0 0 +2				+½	
16								+1							+4	0 +5					

TABLE 1—*Continued*

SERIAL NUMBER	AMOUNT OF OXYGEN IN CUBIC CENTIMETRES																		
	150	200	300	400	450	500	550	600	650	700	750	800	850	900	950	1000	1050	1200	1300	1400	1500
17			0					0 0								0 +1 +1 0		0			
18																0 +1 +2 +1		+1 +2	0		+1
19								+2													
20				+2		+3 0 0 0 0 0		+5 +½ 0		+4			+½		+3	+2 +2 +2 +2 +2 +1 0					
21																+6		+6			
22																0					
23																+2					
24																0					
25																0 +3		+3			
26			+3							+4		0 +3 +3				+3 +4					
27							+2														
28										+1											
29																0					
30								0		0 0	+4					+2					
31			0 0			0 0		0								0					

TABLE 1—*Concluded*

SERIAL NUMBER	AMOUNT OF OXYGEN IN CUBIC CENTIMETRES																			
	150	200	300	400	450	500	550	600	650	700	750	800	850	900	950	1000	1050	1200	1300	1400	1500
32						0										+2					
33								0	0		+½					+½					
34												+1				0 0					
35								0				+3 +1 0				+3 0					
36	0								0 0							0 0					
37													+3	0		+2 0 0 +2 0		0 0 0 0 0			
38												0 +2		0		0 +1					
39										0		0									
40																+4 0					
41									0	0		0		0	0	0					
42																0					
43																		0			0
44										0											

diaphragm decreases in sympatheticotonics and increases in vagotonics; and (5) the type of breathing.

The first four items are self-explanatory. In regard to the last factor, Livingston (6) states that

with distinctly thoracic breathing the general intra-abdominal pressure tends to fall during inspiration; with quiet normal breathing (combined abdominal

and thoracic type) a fall in pressure within the upper abdomen synchronous with inspiration, is still observed; and it is only with breathing of the abdominal type that the general intra-abdominal pressure shows any tendency to rise (increase) during the inspiratory act.

Under normal conditions, in rest there exists a coördination (synergism or antagonistic action) between the diaphragm and the abdominal wall and also between the condition of the abdominal contents and the anterior abdominal wall. The descent (contraction) of the diaphragm is normally associated with a relaxation of the abdominal wall. Similar relaxation is observed following an increase in the volume of the abdominal contents (stomach, tumor, ascites).

It was pointed out by Overholt (8) in his animal experiments that the intraäbdominal pressure which rises following the small injection of air may fail to show a corresponding rise on further injections because of the elasticity of the abdominal musculature. The relaxation of the latter and a distention of the abdomen may counterbalance the tension effect of the injected air. It must be kept in mind also that the irritability of the intestines and the peritoneum, influenced by the stage of a tuberculous process, may induce various grades of reflex contraction of the abdominal muscles in response to the injection of oxygen or air in different persons or occasionally also in the same individual.

Furthermore, the position of the diaphragm and consequently the intraperitoneal pressure may be influenced by the tuberculous involvement of the lungs and pleurae. Massive atelectasis, spontaneous paralysis of the diaphragm on one side, contracting fibrosing tuberculosis, pleural adhesions with an upward displacement of the diaphragm, phrenic-nerve block, thoracoplasty, artificial pneumothorax, and the presence of large pleural effusions must be considered as potential influencing factors in this regard.

When the injection of 600 cc. or more of oxygen was followed by positive pressure (all manometer readings indicate the number of centimetres of the water-column as registered from the zero mark on one arm of the manometer) we noted that (1) the pressure may appear as a nonoscillating one and may remain as such at the close of the inflation; (2) it may appear and remain as an oscillating pressure; and (3) the positive pressure, whether oscillating or not, may disappear following a few respirations. This latter change has been interpreted as a sign of the adaptability of the abdominal wall to the altered intraäbdominal pressure. If

the relaxation of the anterior abdominal wall is proportionate with the increase in the intraäbdominal pressure caused by the injected oxygen, it will cause a return of the pressure to its original level. Such remission was seen in cases in which the pressure was as high as + 5 and in others with lower positive pressures. A rapid return to the preinflation level was observed after the injection of varying amounts of oxygen (500–1000 cc.). It may occur in the same individual on one occasion and may be absent on another. We can offer two explanations for such an occurrence: (1) the prompt relaxation of the abdominal wall and a consequent increase in the abdominal volume, and (2) the major portion of the injected oxygen is drawn up by the subdiaphragmatic negative pressure toward the dome of the diaphragm. This subdiaphragmatic negativity acts in a neutralizing way upon the intraäbdominal pressure increased by the injection of oxygen.

The direction of the manometric oscillations in established pneumoperitoneum corresponds to the motions of the diaphragm, that is, there is a rise of the pressure in the positive direction, parallel with its descent, while the rise of the diaphragm is accompanied by a diminution in the positive pressure. It was noted in 5 cases that the intraäbdominal pressure (following oxygen injection) *decreased on inspiration and increased on expiration.* This phenomenon was designated in a previous paper (1) as *paradoxical oscillation.* Such an occurrence is rather an exception than the rule. It can be explained by the fact that the intrapleural negative pressure is transmitted through the diaphragm to a positive-pressure pneumoperitoneum. The patients showing paradoxical oscillations were fluoroscoped in the upright position immediately following the inflation and it was found that there was no change in the direction of the diaphragmatic motions in relation to respiration, and so the idea of a possible paradoxical excursion of the diaphragm, as seen after paralysis of the phrenic nerve, was discarded.

There are certain symptoms and signs which can be used as reliable indicators of a well-performed artificial pneumoperitoneum. Subjective symptoms: (1) pain in the shoulder region; (2) pain or tightness at the hypochondriac or epigastric area; and (3) abdominal discomfort. Objective symptoms and signs are (1) disappearance of the liver dulness and the presence of tympanitic percussion note instead; (2) the shifting of this tympanitic percussion note according to the position of the patient, namely, when the patient is placed in the Trendelenburg position, the tympany disappears immediately from over the liver and appears in the

pelvic region, while returning the patient to the horizontal position results in the return of the tympanitic percussion note in the right hypochondriac region; and (3) roentgen-ray evidence.

Pain in the shoulder region was practically always present although we have seen patients who did not indicate any pain, not even in the upright position. Therefore, the appearance of shoulder pain may be taken as a sign of arrival of the injected oxygen underneath the diaphragm, but absence of the same type of pain does not exclude the existence of a well-performed pneumoperitoneum. The lower surface of the diaphragm is supplied with a rich network of the terminal branches of the phrenic nerve. The right and left phrenic nerves transmit the pain to the third, fourth and fifth cervical segments. From this area the referred pain is carried through the *nervus cutaneus colli* and the three *nervi supraclaviculares* to the cutaneous areas over the shoulder and the supraclavicular region. Irritation of the right dome of the diaphragm causes pain on the right side, while left-sided pain is noted when the left dome of the diaphragm is irritated.

One would be inclined to believe that the injected gas is evenly distributed in the abdomen and exerts equal pressure upon both domes of the diaphragm. This, however, does not seem to be the case. When a small amount of gas is injected into the abdomen, it collects under the dome of the diaphragm sooner than in any other part of the abdomen in the horizontal position because of the negative pressure continuously present in this area. As a rule, more patients indicated pain in the right than in the left shoulder, although, as a matter of fact, more oxygen collects under the left dome of the diaphragm than on the right side immediately following inflation. However, human beings are accustomed to more or less upward displacement of the left dome of the diaphragm following increase in the volume of the stomach during and after meals. The pressure against the left phrenic dome may thus pass unnoticed. Also in the upright position there might be a shifting of the oxygen from left to right because of the normally higher position of the diaphragm and because of the tendency of gases to occupy the highest available place. Whenever there are present pulmonary or pleural changes, which affect the position of the diaphragm, they may influence indirectly the collection of oxygen on one side or the other. Tuberculous infiltration increases the contractility of the lung. Such a change or extensive atelectasis, a fibrosing pulmonary process, or adhesions, may cause an upward displacement of the diaphragm and the collection of more free gas under

the diseased than under the healthy lung. Yet, in most instances right-sided shoulder pain was complained of. This was the case not only in the average patient, but also, for instance, in women with a two-stage thoracoplasty on the left, in several cases with phrenic-nerve block on the left side, and also in patients with bilateral pneumothorax or with pneumothorax on either side. We think that the cause of this lies, primarily, in the lesser motility of the injected air-column which collects between the liver and the diaphragm, which, not being able to force or indent the solid liver, will exert its pressure more intensively upon the diaphragm. On the other hand, the stomach, being a hollow organ, gives way to the oxygen pressed against it by the descending diaphragm.

As long as the injected oxygen is slowly expanding in the abdomen, no subjective sensation is indicated until the oxygen reaches the subdiaphragmatic area. The penetration of the oxygen to the space between the convexity of the liver and the lower surface of the diaphragm may occur slowly with a consequent gradually increasing consciousness of oxygen being there. In other instances, the patients indicate a rather disagreeable, sudden discomfort underneath the ribs. It is described by them saying "something jerked" or "something snapped." Roentgenograms taken immediately following large inflations have not revealed the existence of adhesions in that area in such instances. It may be reasonably supposed that the cause of such sudden separation of the liver from the diaphragm lies in other factors than in subdiaphragmatic adhesions. A high intrapleural negative pressure transmitted to under the diaphragm, which holds the liver against the lower diaphragmatic surface, might account for this phenomenon. Only three patients reported more pain in the left than in the right shoulder region. In none of them was the cause evident. None had had phrenic-nerve block on the left side; in one of them there was considerably more pulmonary involvement on the left than on the right side.

The change of the percussion note from dull to tympanitic over the right hypochondriac area following the injection of 300 to 400 cc. of oxygen is a useful indicator of a correctly performed inflation. This change is noticeable in every instance, unless adhesions obliterate this area. For the sake of comparison it is well to percuss the same region before the inflation begins, and then repeatedly while the oxygen is injected until the appearance of the tympanitic note. The percussion is carried out by the operator himself by one hand. The injected gas changes its position according to the position of the patient. By lower-

ing the upper part of the body the tympanitic percussion note disappears from over the liver only to become more marked in the upright position. Variations in the percussion note over the liver depend, besides the position, on the amount of gas introduced, upon the relaxation or tension of the abdominal wall, and also upon the time between the injection and examination. The gas being gradually absorbed, the percussion note returns to normal. It was found that following the injection of 600–1000 cc. of oxygen the tympanitic percussion note disappeared in a few days. Roentgenograms, taken at a time when the percussion note returned to normal, still revealed, however, the presence of gas under the diaphragm. The percussion of the left hypochondriac area is not as reliable as that on the right side because of the normally existing tympanitic resonance in that region.

Fluroscopic examination and roentgenograms taken in the *upright position* are the most reliable criteria of the presence of free gas in the abdominal cavity following therapeutic pneumoperitoneum. The rise of the diaphragm is easily visualized in this manner. The direction of the motion of the diaphragm is not influenced, but its extent is diminished. Measurements with regard to the position of the liver and spleen, which under normal conditions are in apposition to the lower surface of the diaphragm, revealed that there is a downward displacement of these organs following the injection of gas. This can be explained (1) by the pressure of the gas injected and (2) by the diminution of the negative subdiaphragmatic pressure, which normally exerts an upward pull upon the subdiaphragmatic organs. The area occupied by the gas does not signify a corresponding upward displacement of the diaphragm, but it is partly made up by a descent of the subdiaphragmatic structures. The importance of this fact is realized when one thinks of the possible diminution in motion of the diaphragm, because of its upward shifting by large amounts of injected gas.

THE SUBPHRENIC ROUTE

The patient is placed in the same position as before artificial pneumothorax. A sand-bag is placed under the lateral aspect of the chest. Local anaesthesia is induced with 1 per cent novocain. The skin is elevated between the index finger and the thumb and nicked with a fine scalpel. A 2.5-inch-long needle, 19 gauge, without an obturator, is used for injection. The needle is connected with the manometer of the pneumothorax apparatus before insertion. The point of entrance of the

needle must be selected below the site of the costophrenic angle. The lower limit of normal pulmonary resonance is higher than the anatomical site of the lower margin of the pleural sack. The following description is given in Gray's Anatomy (9):

> The lines of reflection of the pleurae can be indicated on the surface. On the right side, the lower border crosses the seventh sternocostal articulation, the eighth costochondral junction in the mammary line, the tenth rib in the mid-axillary line, and is prolonged thence to the spinous process of the twelfth thoracic vertebra. On the left side it follows a slightly lower level. [Furthermore, it is stated that] The inferior limit of the pleura is on a considerably lower level than the corresponding limit of the lung, but does not extend to the attachment of the diaphragm, so that below the line of reflection of the pleura from the chest wall on the diaphragm the latter is in direct contact with the rib cartilages and the intercostales interni.

The subphrenic route has been found preferable to the subumbilical injection for several reasons: *1:* The similarity of its technique to that of artificial pneumothorax. This qualifies anyone who is able to perform artificial pneumothorax to give pneumoperitoneum treatment. *2:* The availability of the manometer as an indicator, which registers the site of the point of the needle, as it penetrates near the lower margin of the thorax. *3:* The indication of a properly performed inflation by the early change of the liver dulness into an area with tympanitic percussion. *4:* The patients who are familiar with or are taking artificial pneumothorax submit to this type of treatment more readily than to a subumbilical paracentesis. *5:* The separation of the liver from the dome of the diaphragm is always gradual. Thus the disagreeable feeling occasionally reported by patients, who take oxygen injections by paracentesis of the lower abdominal wall, is avoided; this discomfort originates from the *sudden* penetration of oxygen into the subdiaphragmatic space.

The needle must be introduced slowly and the manometer watched carefully. The manometer, as a rule, indicates negative pressure as soon as the needle passes through the parietal peritoneum. We have encountered only a few cases in which the manometer did not show negative pressure although the point of the needle reached the convexity of the liver. The space between the visceral and parietal peritoneum is a potential cavity like the intrapleural space. Still the introduction of the needle connected with an open manometer shows negative pressure in the subphrenic area. The cause of too close an apposition of the liver

to the diaphragm, which prevents the immediate registration of negative pressure in some cases, is not known to us. The sensation transmitted through the needle, when it glides on the upper surface of the liver during respiration, is very much like the feeling one has when the needle touches a thickened pleura. We are of the opinion that this particular feeling, which is as if the needle would slide over a rough surface, is caused by the normal lobular structure of the liver and not by thickened visceral peritoneum in this area. The manometer shows, invariably, oscillations following the injection of 50 cc. or more oxygen in cases in which no negative reading was obtained when the needle reached the convexity of the liver. Furthermore, oscillations in pressure were seen following small oxygen injections in every case in which the initial negative reading was nonoscillating. According to our experience, the subdiaphragmatic pressure is registered as an oscillating as often as a nonoscillating pressure.

Subatmospheric (negative) pressure was observed in the subdiaphragmatic region by Keppich (10), Melchior (11), Krause (12), and Overholt (8). Riviere (13) states that the subdiaphragmatic pressure varies inversely with the intrapleural pressure during the respiratory phases. Overholt (8) found in animal experiments that the subdiaphragmatic and intrapleural pressures fluctuate in the same direction during respiration and *not inversely*. If we consider the physiological changes in the shape and size of the lower thorax during respiration, it is obvious that the increase in the circumference of the lower thorax is liable to increase the negativitiy in the upper peritoneal cavity rather than to decrease it. We found in the great majority of our cases that the negative subdiaphragmatic pressure became more negative on inspiration and less negative on expiration, that is, its variations coincided with that of the intrapleural negative pressure.

We wish to record two deviations from these observations:

V. H. (group 2, case 56) was given repeated oxygen injections by the subdiaphragmatic method. An oscillating negative pressure was found on each occasion. At the time of the last inflation no manometer reading was registered when the needle reached the convexity of the liver. Following the injection of 100 cc. of oxygen, -3 pressure was noted. The pressure was fluctuating *opposite* to the intrapleural pressure, that is, it became more positive on inspiration and less positive on expiration. When 250 cc. were injected, the manometer showed -0.5 and the pressure was changing identically with the intrapleural variations. The inflation was closed with a reading of $+1.5$;

the oscillations followed that of the intrapleural pressure. *J. T.* (case 8479), not included in the 100 analyzed cases, was given his first pneumoperitoneum treatment. No manometer reading was obtained, when the needle touched the upper surface of the liver. Following the injection of 50 cc. of oxygen, an oscillating positive pressure, +4, was recorded. The reading changed to more positive on inspiration. After the injection of 450 cc. of oxygen an oscillating positive pressure, +7, was noted. It was increasing on inspiration and decreasing on expiration.

The amount of oxygen injected by the subdiaphragmatic method should be adapted to the immediate subjective response of the patient. It varies between 400 and 1500 cc. It was emphasized before that undue tension by too large quantities of oxygen should be avoided. The abdomen should be rather underinflated than overinflated. When intense shoulder pain is complained of after treatment, the patient should be taken to his room on a cart. The foot of the bed should be elevated in every case for the next two days. The injected air is shifted from under the diaphragm toward the pelvis and thus the pressure on the diaphragm and consequently the shoulder pain are immediately relieved by this simple measure.

Minor discomfort, such as pain in the lower thoracic region and reflex nausea, was seen occasionally, but proved to be of short duration. In some of the patients who had had considerable expectoration prior to this treatment, the expectoration was increased as soon as the discomfort from tension disappeared.

We have not encountered any serious accident, such as peritoneal shock, haemorrhage from the deep epigastric or mesenteric blood-vessels, perforation of an intestine, air emobolism or peritonitis.

PNEUMOPERITONEUM AND PHRENIC-NERVE BLOCK FOR THE TREATMENT OF PULMONARY TUBERCULOSIS

There are a great many instances in which, because of pleural adhesions, no artificial pneumothorax can be produced. The result of phrenic-nerve block is often unsatisfactory in such cases. Thoracoplasty may be contraindicated, or it may be indicated but refused by the patient. The combination of phrenic-nerve block with pneumoperitoneum should be resorted to in such cases. This suggestion is made on the basis of the therapeutic response we have seen in one of our cases and also because it is logical to attempt to collapse the lung by an air-splint below the diaphragm, when such collapse cannot be carried out by other means. Con-

siderable elevation of the dome of the diaphragm often follows phrenic-nerve block, even if extensive pleural adhesions are present. This elevation can be effectively increased by pneumoperitoneum, injecting 700–1000 cc. of oxygen or air, preferably through the subdiaphragmatic route. The injections are repeated at weekly intervals, thus preserving a sufficient amount of free gas in the peritoneal cavity to sustain the desired elevated position of the diaphragm and consequently a satisfactory collapse of the diseased lung. It is of great advantage, if the patient's general and pulmonary condition allow, to have him lie on the healthy side. If this is done, all the injected gas will collect in the uppermost part of the abdomen, that is, under the dome of the diaphragm on the diseased side, thus accomplishing the maximum upward displacement of the diaphragm on that side.

Report of a Case

M. B., case 7086 (not included in the 100 cases analyzed): Far-advanced pulmonary tuberculosis, involving the upper and lower one-thirds of the right lung and the entire left lung. Exairesis of the left phrenic nerve was performed April 2, 1931. The left dome, which prior to the operation occupied the same level as the right dome of the diaphragm (level of upper margin of the 10th rib posteriorly), was found one finger's breadth higher immediately after operation. The subsequent clinical changes were not satisfactory. Because of an alarming haemorrhage artificial-pneumothorax treatment was decided upon, in spite of the fact that such attempts ended in failure prior to the phrenic-nerve block because of extensive pleural adhesions. The patient was given eight inflations, the amounts of air varying from 100 to 800 cc. The final manometer readings were four times on the positive side,—once as high as +7 and once +9. The patient had pleural shock on one occasion. At the ninth attempt the initial manometer reading was −5 and the inflation was closed with a −1 reading after the injection of 1000 cc.

Subsequent roentgenograms showed that an artificial pneumoperitoneum was performed instead of the intended artificial pneumothorax. Technical details of this case were reported in another paper dealing with incidental pneumoperitoneum (14). The benefits of this treatment were noticed by the patient as well as by the attending staff. The massive pulmonary haemorrhage was checked and the appetite and general condition improved. The roentgenograms revealed findings of some interest. Both domes of the diaphragm were elevated. The left dome was higher than the right, occupying the level of the lower margin of the 9th rib posteriorly. Double-exposure plates taken before and after the injection of oxygen showed an increased limitation in the motion of the ribs over the lower one-third of the chest. Under normal con-

ditions, placing a person on the lateral recumbent position is followed by a rise of the lower and a descent of the uppermost dome of the diaphragm. A roentgenogram taken with the patient lying on his right side showed the left dome of the diaphragm in the 8th interspace posteriorly. The difference between this and its level prior to this treatment is 41 mm.

It is of prime importance from the standpoint of therapeutic approach of otherwise intractable cases of pulmonary tuberculosis that such a rise in the level of the diaphragm can be produced by a therapeutic pneumoperitoneum. The higher the elevation of the diaphragm the better are the chances for the restriction of the respiratory excursions in addition to other healing potentialities associated with a successful collapse of the diseased lung.

Because most of the cases which would fall into a group suitable for this treatment are of long-standing and obstinate types of tuberculosis, it seems advisable to perform a permanent phrenic-nerve block (exairesis or phrenicectomy). The nerve block should be done prior to the pneumoperitoneum.

Roentgenological observations were made on three more patients who had had phrenic-nerve block prior to pneumoperitoneum. Altogether we have had 9 patients treated by the combination of these two procedures. Unfortunately, the pneumoperitoneum treatment was not carried on long enough or consistently enough to enable us to esitmate its therapeutic value except in the case described above.

Primary contralateral pneumothorax has been advocated by Ascoli (15) for the treatment of cases in which extensive pleural adhesions prevented the introduction of air on the diseased side. Relying on improvements in both lungs seen in bilateral pulmonary tuberculosis, following unilateral artificial pneumothorax, an attempt to influence a diseased lung by collapsing the opposite (healthy) side seemed to be feasible. The "collapse" and "immobilization" were attained by the shifting of the mediastinum toward the diseased side. We believe that a better collapse and immobilization can be established by artificial pneumoperitoneum than by primary contralateral pneumothorax, provided the inflations are repeated at weekly intervals for the sustenance of the upward displacement of the diaphragm. Artificial pneumoperitoneum causes only a slight loss of the respiratory function of the healthy lung, particularly if the patient is kept on proper postural rest (shifting the air underneath the affected lung). Also, the difficulty of encountering pleural adhesions

or inducing subsequent fluid-formation is avoided by establishing collapse by phrenic-nerve block, supported by artificial pneumoperitoneum.

We think that periodically repeated artificial pneumoperitoneum should be considered as a supportive measure in all cases of artificial pneumothorax in which the collapse of the basal portion of the lung is desirable, but cannot be accomplished by pneumothorax alone, because of adhesions. The upward displacement of the corresponding side of the diaphragm and the consequent curative effect upon the diseased lung may equal that of a phrenic-nerve block.

The rapidity of absorption of the injected oxygen is of great importance in this regard. Whenever a sustained elevation of the diaphragm is aimed at, the intervals between reinflations should depend on the rapidity of absorption. The latter is influenced by the amount of injected gas and the thickness of the peritoneum. The large peritoneal surface and the fact that the gaseous tension of the blood is one-tenth that of the atmosphere are primarily responsible for the elimination of injected gases. The diffusion of oxygen through a thickened peritoneum is slower than when the peritoneum is normal. We found that the longer the injections are continued, the less rapid is the absorption of oxygen. An attempt to determine the presence or absence of free oxygen in the peritoneal cavity by percussion may be misleading. It seems that the roentgen-ray is the only means to determine correctly how long the injected gas will stay in the peritoneal cavity. Serial roentgenograms clearly demonstrated the gradual absorption of oxygen. For instance,

in case 7086 (*M. B.*), 500 cc. were injected on April 29, 1932. The diameter of the gas-pocket under the diaphragm in the midclavicular line was 22 mm. on the right and 59 mm. on the left side immediately following inflation. Measurements of the same, a week later, were 15 mm. on the right and 25 mm. on the left side. Case 35 (group 2) was given 1500 cc. on July 8, 1932. The width of the oxygen pocket under the diaphragm was 57 mm. on the right and 85 mm. on the left side. Corresponding measurements were on July 11, 1932: right, 37 mm., and left, 24 mm., and on July 15, 1932, right, 13 mm., and left, 16 mm. No free oxygen was detectable two weeks after inflation.

In cases in which we attempt to influence therapeutically intestinal or peritoneal tuberculosis it is not necessary to determine accurately the persistence of oxygen, because the results are dependent upon the secondary hyperaemia induced by the oxygen rather than on the prolonged presence of oxygen. The intervals are set arbitrarily at every two weeks, but may vary according to symptoms or the therapeutic response.

Artificial pneumoperitoneum has palliative as well as curative value. Most striking is the decrease in the number of stools, recurrence of formed

TABLE 2

Duration and character of therapeutic response

RESULTS	FIRST GROUP		SECOND GROUP		BOTH GROUPS	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Improved	31	70.4	40	71.4	71	71.0
Unimproved	13	29.6	16	28.6	29	29.0
No recurrence			14	25.0		
Recurrence			26	46.4		
Complete relief	14	31.8	20	35.7	34	34.0
Partial relief	17	38.6	20	35.7	37	37.0

TABLE 3

Therapeutic response as related to the number of inflations

			NUMBER OF INFLATIONS											
			1	2	3	4	5	6	7	8	9	10	12	20
First group	Improved		7	7	3	3	4	2	2	1			1	1
	Unimproved		7	2		1	1	1		1				
	Total		14	9	3	4	5	3	2	2			1	1
Second group	Improved		7	10	6	4	5	1	2	2	1	1	1	
	Unimproved		10	4	2									
	Total		17	14	8	4	5	1	2	2	1	1	1	
Both groups	Improved	Cases	14	17	9	7	9	3	4	3	1	1	2	1
		Per cent	45.2	73.9	81.8	87.4	90.0	75.0	100	75.0	100	100	100	100
	Unimproved	Cases	17	6	2	1	1	1		1				
		Per cent	54.8	26.1	18.2	12.6	10.0	25.0		25.0				
	Total		31	23	11	8	10	4	4	4	1	1	2	1

stools, and the disappearance or amelioration of disagreeable gastro-intestinal symptoms, particularly abdominal pain. One can readily see that by restoring normal digestive function the nutrition and recovery

TABLE 4

Therapeutic response in relation to gastrointestinal symptoms (Second group)

SERIAL NUMBER	NAME	AGE IN YEARS	SEX	PULMONARY FINDINGS ACCORDING TO TURBAN		ANOREXIA	GASTRIC DISTRESS	NAUSEA	VOMITING	ABDOMINAL PAIN	CONSTIPATION	DIARRHOEA	INTESTINAL HAEMORRHAGE	SYMPTOMATIC RELIEF				UNIMPROVED	NUMBER OF INFLATIONS
				R	L									Complete	Partial	No recurrence	Recurrence		
1	I. R.	45	F	III	I					+		+		+			+		5
2	A. O.	20	F	I	I	+			+			+						+	2
3	S. S.	35	F	III	II			+	+	+				+		+			1
4	P. C.	35	M	III	II		+		+	+								+	1
5	N. S.	43	F	II	II		+	+	+	+					+		+		1
6	A. E.	24	F	III	II					+		+		+			+		4
7	M. L.	26	F	I	II					+		+	+		+		+		2
8	O. S.	42	M	III	II		+	+	+			+						+	1
9	L. G.	22	F	–	–				+	+								+	2
10	A. P.	21	F	III	II		+	+	+	+					+	+			5
11	S. B.	22	F	III	II	+		+		+		+						+	3
12	C. G.	27	M	0	I					+					+		+		2
13	E. L.	19	F	III	II			+	+	+								+	1
14	A. K.	25	F	III	II		+			+					+		+		10
15	M. A.	14	F	II	I			+	+	+		+			+		+		3
16	W. S.	18	F	I	II					+		+		+			+		7
17	J. M.	26	M	I	II		+			+	+	+			+		+		3
18	R. W.	21	F	I	I							+		+			+		9
19	J. B.	39	M	III	II		+	+		+	+				+	+			1
20	F. B.	24	F	0	II			+		+	+	+		+			+		2
21	S. S.	34	M	III	II		+			+				+		+			3
22	H. F.	21	M	0	II					+		+			+		+		1
23	P. S.	25	F	II	II	+		+		+				+		+			1
24	W. M.	27	M	II	II	+	+	+				+						+	2
25	R. G.	30	M	II	II		+		+	+		+			+	+			2
26	A. B.	26	M	–	–		+			+		+						+	1
27	R. S.	29	M	II	0		+			+		+			+	+			4
28	A. B.	23	F	II	0					+		+		+		+			5
29	E. B.	36	F	II	II	+				+		+			+		+		12
30	S. G.	30	M	I	I					+		+		+		+			3
31	E. F.	31	M	I	I					+				+		+			2
32	A. J.	26	F	I	II	+	+	+		+	+	+			+		+		5
33	M. S.	38	F	III	I		+			+		+		+			+		2
34	M. M.	45	F	0	II	+		+		+				+			+		7
35	T. G.	20	F	I	0	+	+			+		+		+		+			8
36	B. A.	32	F	III	0		+			+		+		+			+		6
37	G. S.	28	F	I	0		+			+				+			+		2
38	P. W.	26	F	I	0					+		+		+			+		3

TABLE 4—*Concluded*

SERIAL NUMBER	NAME	AGE IN YEARS	SEX	PULMONARY FINDINGS ACCORDING TO TURBAN		ANOREXIA	GASTRIC DISTRESS	NAUSEA	VOMITING	ABDOMINAL PAIN	CONSTIPATION	DIARRHOEA	INTESTINAL HAEMORRHAGE	SYMPTOMATIC RELIEF				UNIMPROVED	NUMBER OF INFLATIONS
				R	L									Complete	Partial	No recurrence	Recurrence		
39	M. M.	23	F	III	II			+	+			+			+		+		2
40	J. G.	34	M	II	I	+	+			+		+						+	1
41	E. W.	41	M	III	I		+			+		+						+	1
42	M. S.	22	F	III	II					+		+						+	1
43	M. T.	26	F	III	II					+		+						+	2
44	G. W.	43	M	III	II	+				+		+						+	1
45	V. O.	28	M	–	–		+	+			+							+	3
46	E. I.	22	F	III	II				+		+	+			+		+		1
47	S. D.	23	F	II	II	+				+		+			+		+		2
48	J. K.	28	M	0	II		+			+		+			+		+		8
49	A. E.	20	F	II	II	+				+				+		+			4
50	L. W.	18	F	I	II			+		+		+						+	1
51	A. G.	27	F	I	II				+	+		+						+	1
52	J. M.	44	M	II	II	+						+			+	+			1
53	S. B.	21	F	III	II					+		+		+		+			2
54	M. K.	43	F	III	I	+	+								+		+		5
55	F. W.	25	F	II	II	+	+			+				+			+		3
56	V. H.	25	F	II	II					+		+			+		+		4

of the patient can be helped, especially when the patient's general resistance is still good and the pulmonary lesion is not hopelessly advanced. The frequency of intestinal tuberculosis as a complication of pulmonary tuberculosis obligates the profession to a more frequent application of this measure.

Incidental benefits of this treatment are also of value. Patients, whose diarrhoea is checked, rest better during the day and sleep better during the night. Many of them experience an immediate euphoria which may be due to absorption of the oxygen. The psyche is also favorably influenced as soon as symptomatic relief is produced in this apparently untractable and dreaded complication. Goodman (16) reported an increase in the number of red blood corpuscles following intraperitoneal oxygen injection. Boller (17) found an increase in the number of leucocytes in 17 out of 22 pneumoperitoneum cases. He explains this leucocytosis as a sympathetic effect provoked by the upward displacement of the diaphragm and by a transference of stimulation through the

TABLE 5

Duration of gastrointestinal symptoms, and extent and duration of pulmonary tuberculosis in relation to therapeutic results

(First group)

SERIAL NUMBER	PATIENT	AGE	SEX	PULMONARY TUBERCULOSIS ACCORDING TO TURBAN		DURATION OF GASTRO-INTESTINAL SYMPTOMS (IN MONTHS)	DURATION OF PULMONARY TUBERCULOSIS (IN YEARS)	CHANGE IN THE GASTRO-INTESTINAL CONDITION			NUMBER OF INFLATIONS
								Improved		Unimproved	
				R	L			Complete	Partial		
1	F. H.	53	M	III	II	1	6	+			2
2	W. R.	27	M	II	II	4	1½		+		5
3	M. S.	30	M	III	II	24	3	+			1
4	P. W.	26	M	II	II	6	3	+			2
5	S. S.	29	F	III	II	3	2		+		7
6	C. O.	24	M	III	II	1	⅔			+	1
7	R. C.	44	M	III	II	9	5	+			2
8	J. M.	52	M	III	II	6	14	+			4
9	M. S.	21	F	III	II	3	2		+		4
10	F. A.	46	M	III	II	8	13			+	1
11	M. C.	37	M	III	II	11	6		+		1
12	A. B.	39	M	III	II	7	10			+	1
13	G. D.	54	M	III	II	10	7		+		3
14	D. B.	17	F	I	II	5	1			+	2
15	R. N.	21	M	III	II	3	2		+		5
16	A. K.	23	M	III	II	1	1			+	4
17	A. L.	19	M	III	II	7	6		+		8
18	F. G.	19	M	II	II	2	1			+	8
19	A. H.	39	F	I	II	8	4			+	1
20	M. H.	29	F	III	II	14	10	+			20
21	K. F.	45	M	III	II	2	5			+	2
22	L. R.	21	M	0	II	3	3			+	1
23	C. N.	29	F	III	II	1	½			+	1
24	M. Z.	31	M	III	II	5	1	+			1
25	R. M.	27	M	I	II	3	⅔		+		3
26	H. B.	21	F	II	II	2	2	+			7
27	B. P.	23	F	III	II	4	1		+		1
28	F. S.	19	F	III	II	2	14		+		1
29	J. W.	30	M	III	II	2	1½	+			1
30	B. W.	22	F	III	II	6	⅔	+			5
31	W. K.	48	M	III	II	7	3		+		6
32	J. P.	57	M	II	I	2	1	+			2
33	J. G.	27	M	III	0	1½	1	+			4
34	M. W.	37	F	III	II	3	3		+		3
35	M. S.	18	F	III	II	2	1			+	6
36	E. B.	23	M	III	I	9	1		+		5
37	B. S.	38	F	III	II	14	7		+		12
38	G. S.	37	M	III	I	3	5			+	5
39	R. B.	26	M	II	II	5	2	+			2
40	J. S.	42	M	II	II	7	4		+		2
41	T. P.	18	M	I	II	6	1½		+		6
42	D. P.	21	F	II	I	2	1		+		1
43	W. K.	21	F	III	II	1	1	+			2
44	H. O.	34	F	III	II	12	6			+	1

phrenic nerves. The analysis of the roentgenological findings indicate that the therapeutic results are not proportionate to the extent of the intestinal involvement. Symptomatic relief was seen in cases in which the entire colon was affected, while in other instances no favorable response was obtained, although the disease was limited to a small portion of the intestine.

We wish to record a few additional observations that might be of some practical value. Artificial pneumothorax, unilateral or bilateral, is not a contraindication. Patients with phrenic nerve-block on one side, or on both sides, tolerate oxygen injection well. We have had two cases of thoracoplasty successfully treated by repeated inflations. No treatment should be given during menstruation, because it might cause severe contractions of the uterus. One finds cases occasionally, in which tightness in the chest or heart discomfort is complained of. These symptoms are promptly relieved by elevating the foot of the bed. Abdominal distention or tension, if present, usually disappears in a few days. The inflation must be done slowly to avoid sudden distention of the abdomen. Sometimes the bore of the needle is obstructed by the omentum or the intestinal wall. There is no flow or only very slow flow of oxygen in such cases. The withdrawal and reinsertion of the needle will correct this situation. Peritoneal adhesions might cause severe pain after the injection of small amounts of gas. The manometer indicates wide oscillations on the positive side in such instances.

Pneumoperitoneum does not cause the formation of adhesions. On the contrary, it has a tendency toward breaking-up adhesions. One such instance was reported in a previous paper (1). Carnot (18) suggested therapeutic pneumoperitoneum to prevent adhesions following intestinal resection. Also, Gellhorn (19) recommended the injection of air or oxygen into the abdomen, when adhesions were present at the operation, to break up these adhesions and prevent their formation.

We have treated two cases of intestinal haemorrhage, originating from tuberculous ulcer. The haemorrhage was stopped in one of them, but it could not be controlled in the other.

SUMMARY

1. Therapeutic pneumoperitoneum has proved to be a technically simple and practicable treatment for intestinal tuberculosis.

2. The subphrenic method is far superior to paracentesis elsewhere of the anterior abdominal wall.

3. The intraperitoneal pressure is neutral below the umbilicus and negative (subatmospheric) in the subdiaphragmatic region.

4. The negative subdiaphragmatic pressure parallels the changes of the intrapleural pressure, that is, it becomes *more negative* on inspiration and *less negative* on expiration.

5. The rise in the intraperitoneal pressure following the injection of oxygen is not necessarily proportionate with the injected amount.

6. The increased intraperitoneal pressure often returns to neutral after few respirations, even when large amounts of oxygen were injected, because of the accommodation of the abdominal wall and the diaphragm.

7. Properly performed pneumoperitoneum is recognized by certain symptoms, such as shoulder pain, pain or tightness in the hypochondriac region, abdominal discomfort, and by certain signs, such as disappearance of the liver dulness, shifting of the suprahepatic tympanitic percussion note, according to the position of the patient, and roentgen-ray evidence.

8. The therapeutic feasibility and practicability of long-continued pneumoperitoneum in combination with exairesis of the phrenic nerve is suggested and discussed for the treatment of otherwise intractable cases of pulmonary tuberculosis, in connection with one of our cases thus treated.

9. The analysis of the therapeutic results in 100 cases of intestinal tuberculosis treated by pneumoperitoneum indicates that 29 per cent had no benefit from it, while symptomatic relief (complete or partial, lasting or temporary) was observed in 71 per cent.

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A SCALENIOTOMY DIRECTOR[1]

J. W. CUTLER

The proper retraction of the scaleni muscles and the safe-guarding of vital structures are the most important considerations in the skilful and speedy completion of scaleniotomy for pulmonary tuberculosis. To attain these ends I have designed the instruments illustrated here and have found them entirely satisfactory.

The specially designed grooved director makes it possible to elevate the scaleni into full view, where they can be cut without danger of injury

FIG. 1. SCALENIOTOMY DIRECTOR[2]

The instruments are grooved and are made of opposite curves (A and B) in order to facilitate technique.

to surrounding important structures. The angle of the handle is such as to facilitate the easy passage of the instrument beneath the muscle without undue effort on the part of the operator. In order to protect the vital structures still further, particularly the brachial plexus, the instruments have been designed with opposite curves (A and B) so that the operator can always work away from the plexus in passing the grooved director beneath the muscles without having to change his position at the operating table. Furthermore, the use of these instruments permits the cutting of the scaleni muscles through the smallest possible incision.

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

[2] This instrument is made by The George P. Pilling and Son Co., Philadelphia.

CHANGES IN PULMONARY TUBERCULOUS CAVITIES RESULTING FROM INDUCED PARALYSIS OF THE DIAPHRAGM[1,2]

PAUL SLAVIN

The behavior of pulmonary tuberculous cavities following phrenic-nerve interruption can be properly traced, provided the cavity shadows are clearly outlined on successive roentgenograms. Selection of the cases discussed in this paper was guided by the graphic fitness of the cavity shadows for simplified measuring on serial roentgenograms.

Changes that could be attributed to induced paralysis of the diaphragm occurred only in cavities enclosed within functioning lung tissue and located in a lobe with little or no parenchymal involvement outside the cavity. All other cavities appeared to follow their original course without showing obliterative tendencies. Cavities surrounded by functioning lung tissue are constantly acted upon by the respiratory movement of the lung. On each inspiration the fibrous tissue in the vicinity of the cavity is being stretched by the expanding lung. The cavity-walls are prevented from retraction and condensation and remain thin. The immediate changes, appearing in those cavities after the phrenic paralysis, are produced by two factors: (1) compression exerted by the elevated diaphragm and (2) relaxation resulting from cessation of diaphragmatic movements. Sudden elevation of the paralyzed diaphragm lessens the vertical capacity of the hemithorax and the treated lung adjusts itself by undergoing partial collapse in its oblong diameter. This compression is unevenly distributed throughout the lung, diminishing in its extent from below upward, with a predilection for diseased areas deprived of elasticity. The thin-walled cavity is flattened upward. There is usually a simultaneous expansion of the cavity in its transverse direction, so that the cavity-space is not much diminished. Tilting of the cavity may take place, with trapping of the sputum due to torsion of the draining bronchus.

[1] From the New Jersey Sanatorium for Tuberculous Diseases, Glen Gardner, New Jersey.

[2] Presented at the 10th Fall Meeting of the Eastern Section of the American Sanatorium Association, Lakeland, New Jersey, October 6–7, 1933.

The paralyzed diaphragm ceases to descend on inspiration and the range of the respiratory changes in the volume of the hemithorax becomes reduced. A motive force for expansion of the lung is removed. Tugging on the cavity-walls decreases, allowing the fibrous tissue around the cavity to contract. As a result the cavity-rim shows measurable widening and condensation soon after the operation.

The subsequent changes developing in those cavities within a varying prolonged period of time represent the outcome of continued relaxation. The cavity's capsule, partly relieved of the tension caused by the expanding surrounding lung, undergoes gradual generalized contraction, obliterating the cavity-space in a concentric manner. There is no evidence of further upward compression of the cavity though the diaphragm is subject to successive rises. It is probable that the secondary rises of the paralyzed diaphragm are the result and not the cause of continued diminution in the volume of the treated lung. They are compensatory in character, serving to fill part of the vacant space created in the hemithorax by fibrotic contraction of defects and atelectatic processes in the relaxed lung. The highest rise of the diaphragm is seen in cases with extensive disease outside the cavity, the diseased areas being less resistant to atelectasis than healthy lung tissue. The cavities in those cases are not influenced by induced paralysis of the diaphragm.

The ultimate closure of cavities responsive to phrenic-nerve interruption and the length of time required for the obliterative process are not controlled by the amount of elevation of the paralyzed diaphragm, but depend on the size and location of cavity, and upon the condition of the contralateral lung. The size of the cavity is determined on the films by the diameters of the flat cavity shadows. The depth of the cavity can be judged only by the degree of rarefaction of the cavity shadow and by preservation of lung markings within it. The deeper portions of the cavity are more translucent to the roentgen-rays and a cavity shadow may present areas of various densities. The depth of the cavity has a distinct bearing on its healing. The tendency to obliterate under induced paralysis of the diaphragm, while apparent in shallow cavities, is retarded or absent in deep excavations. The capacity to heal is generally lessened and slower in large defects.

The nearer the cavities are situated to the base of the lung the more is the initial collapse caused by rise of the paralyzed diaphragm.

The degree of relaxation of the treated lung is modified by the state of the contralateral lung. If the latter is not competent to provide an

adequate breathing volume, the accessory muscles of respiration on the treated side come into play substituting the diaphragm. The relaxing effect of the phrenic interruption is then nullified.

Cases

1: No. 10,958, H. B., male, aged 31 years. On admission right lung showed cavity, 4.7 x 5 cm., located centrally in upper lobe, and area of fibrosis and tuberculous infiltration adjacent to lower cavity-wall. Rest of lung field surrounding cavity appeared to be clear (figure 1, September 12, 1929). Sputum positive for tubercle bacilli. Artificial pneumothorax attempted repeatedly but no free pleural space found. The cavity did not show any obliterative changes on routine rest-cure, and phrenicectomy was performed six and a half months after admission. Figure 2, 12 days after the operation, shows paralyzed diaphragm elevated 4.6 cm.: vertical diameter of cavity shortened 1 cm., apparently through upward compression; transverse diameter decreased 0.2 cm. *Sputum-level in cavity.* On figure 3, 6½ months after operation, the cavity is obliterating concentrically, with both diameters equally diminished. Diaphragm is 0.3 cm. lower than on previous plate. Sputum became negative 4½ months after operation. Figure 4, one year after operation, shows annular shadow, 2 x 2 cm., opaque, dense, and representing remainder of cavity filled with fibrous tissue. Calcification and fibrosis in place of infiltration below cavity. Diaphragm elevated 5.2 cm. On figure 5, three years after operation, the former lesion is replaced by calcification and fibrosis. For last three years the patient is working full-time.

2: No. 10,966, J. K., male, aged 35 years. On admission, September 24, 1929, right lung showed two adjoining cavities occupying practically entire upper lobe. Sputum positive for tubercle bacilli. Figure 6, February 17, 1930, shows same cavities five months later. Both are situated near periphery of chest, and completely surrounded by lung field. The lower cavity is sharply defined, measuring 4 x 5 cm. Patient continued on rest-cure for eleven months, during which there were repeated haemoptyses, continuous toxic manifestations, and profuse bacillary expectoration. Because of certain objections in this case to prolonged pneumothorax treatment, phrenicectomy performed August 11, 1930. On figure 7 the lower cavity shadow is flattened upward, tilted and expanded horizontally, measuring 4.5 x 4.5 cm. Cavity-rim thicker and more accentuated in both cavities. Diaphragm elevated 4 cm. Two months after operation (figure 8, October 21, 1930) both cavities obliterating concentrically, with lower cavity measuring 2.5 x 3.2 cm. Paralyzed diaphragm elevated 4.7 cm. Figure 9 shows disappearance of both cavities seven and a half months after operation. Diaphragm only 3.2 cm. elevated. Patient working full-time for last two and a half years.

3: No. 12,604, H. S., male, aged 23 years. On admission, May 31, 1932, there was a cavity in right upper lobe, 2 x 2.5 cm., located centrally, with area of tuberculous infiltration adjoining outer lower aspect of cavity-rim. Rest of lung-field surrounding cavity appeared clear. Sputum positive for tubercle bacilli. Artificial pneumothorax attempted but no free pleural space found. After five months of rest-cure the cavity space showed increase in size through continued destruction within adjacent area of infiltration, and then measured 3.0 x 3.0 cm. (figure 10, October 24, 1932). Temporary phrenic interruption performed October 25, 1932, and figure 11, two days after operation, shows cavity displaced and flattened upward, its rim thickened, its transverse diameter increased. Upward displacement of cavity due to vertical contraction of upper lobe. Paralyzed diaphragm elevated 2.6 cm. On figure 12, two months after operation, diaphragm is still higher, and the cavity is diminished in both vertical and transverse directions. Cavity-wall confluent with surrounding scar-tissue. Figure 13, three months after the operation, shows disappearance of cavity.

4: No. 12,848, J. B., male, aged 27 years. Admitted October 17, 1932, with bilateral cavitation, cavity in right upper lobe measuring 3.5 x 4 cm., and in left upper 2 x 2 cm. Both cavities, though situated near periphery of chest, completely surrounded by lung-tissue. Small areas of tuberculous infiltration scattered throughout both lung-fields (figure 14). Sputum positive for tubercle bacilli. Three months of rest-cure did not change size of cavities, and phrenicectomy was performed on right side, the seat of the larger cavity. Figure 15 shows treated cavity two days after the operation, compressed upward, tilted, and with thicker walls. Diaphragm elevated 4.5 cm. On figure 16, one month after operation, treated cavity shows concentric obliteration, being equally diminished in both transverse and vertical diameters and measuring 2.5 x 3 cm. Diaphragm elevated 5.1 cm. Figure 17 shows disappearance of cavity three months after operation. In place of former annular rarefied shadow there is a dense opaque shadow, presenting apparently the cavity-space filled with fibrous tissue. The left cavity shadow is larger. Figure 18, eight months after admission, presents a selective pneumothorax collapse of the left upper lobe with the left cavity shadow accentuated. Cavity on right not reopened. In this case the larger cavity became obliterated through phrenic-nerve interruption, while the smaller cavity in the nontreated lung grew larger.

5: No. 9,070, J. S., male, aged 35 years. Admitted to Sanatorium seven and a half years ago with extensive tuberculous involvement of both lungs. Continuously on rest-cure since that time. Profuse bacillary expectoration. Figure 19, five years after first admission, shows in right midlung region a flattened cavity, measuring 5 x 3 cm. On figures 20 and 21, eighteen and twenty-two

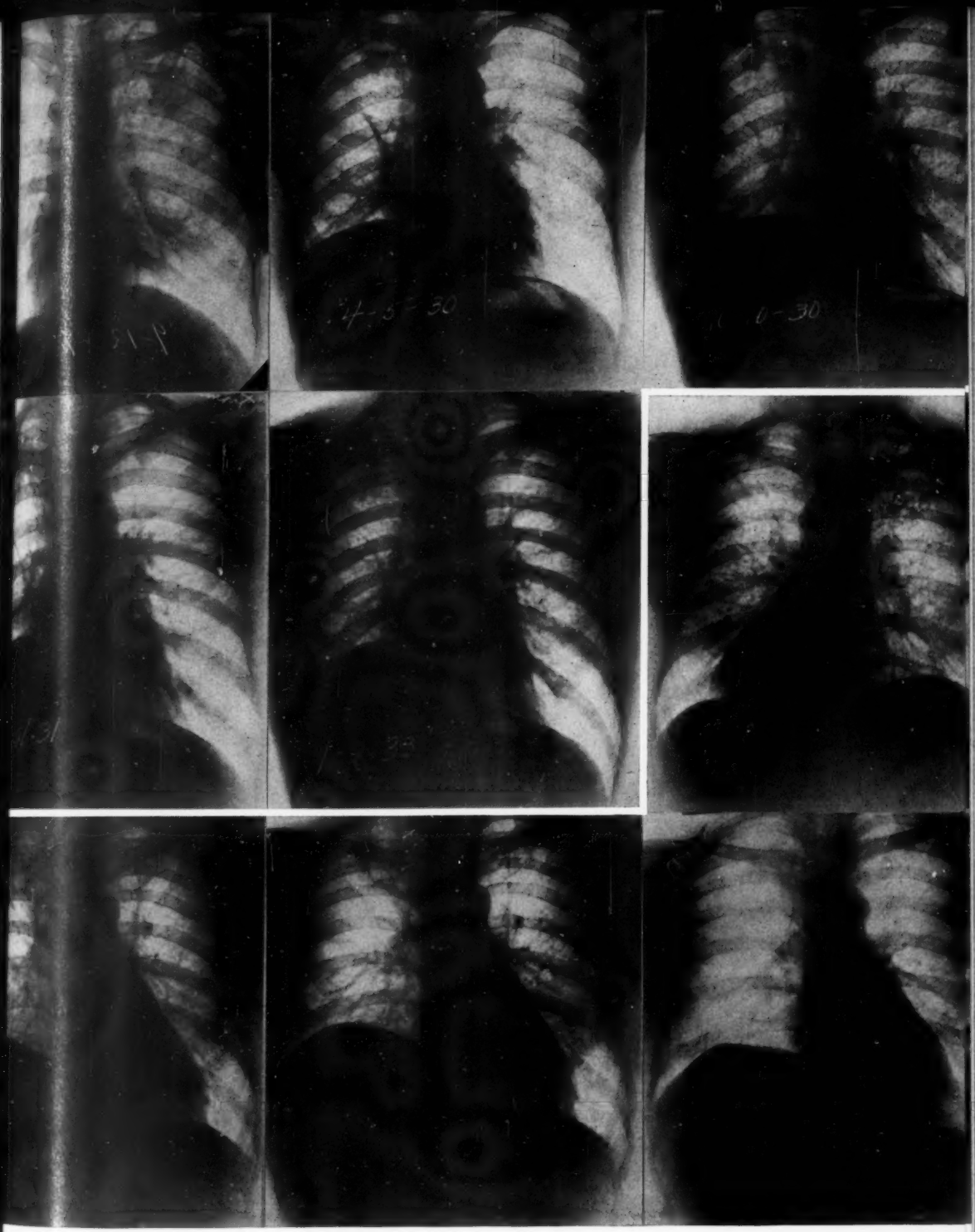

FIG. 1	FIG. 2	FIG. 3
FIG. 4	FIG. 5	FIG. 6
FIG. 7	FIG. 8	FIG. 9

PLATE 1

FIG. 1. Case 1 (a). H. B. September 12, 1929.
FIG. 2. Case 1 (b). H. B. April 5, 1930.
FIG. 3. Case 1 (c). H. B. October 10, 1930.
FIG. 4. Case 1 (d). H. B. March 26, 1931.
FIG. 5. Case 1 (e). H. B. January 2, 1933.

FIG. 6. Case 2 (a). J. K. February 17, 1930.
FIG. 7. Case 2 (b). J. K. August 23, 1930.
FIG. 8. Case 2 (c). J. K. October 21, 1930.
FIG. 9. Case 2 (d). J. K. March 19, 1931.

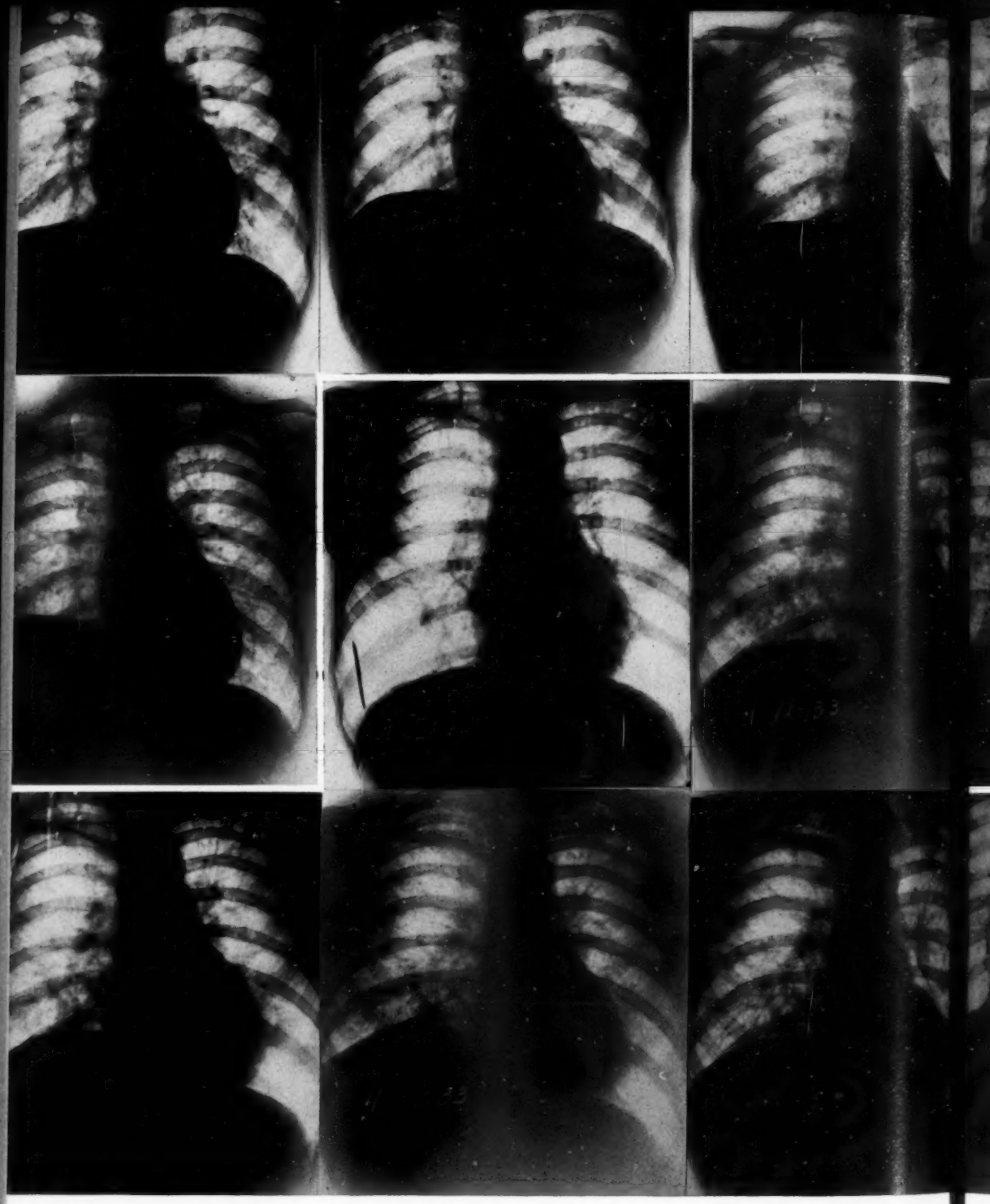

FIG. 10	FIG. 11	FIG. 12
FIG. 13	FIG. 14	FIG. 15
FIG. 16	FIG. 17	FIG. 18

PLATE 2

FIG. 10. Case 3 (a). H. S. October 24, 1932.
FIG. 11. Case 3 (b). H. S. October 27, 1932.
FIG. 12. Case 3 (c). H. S. December 30, 1932.
FIG. 13. Case 3 (d). H. S. January 30, 1933.
FIG. 14. Case 4 (a). J. B. October 20, 1932.
FIG. 15. Case 4 (b). J. B. January 12, 1933.
FIG. 16. Case 4 (c). J. B. February 14, 1933.
FIG. 17. Case 4 (d). J. B. April 14, 1933.
FIG. 18. Case 4 (e). J. B. June 16, 1933.

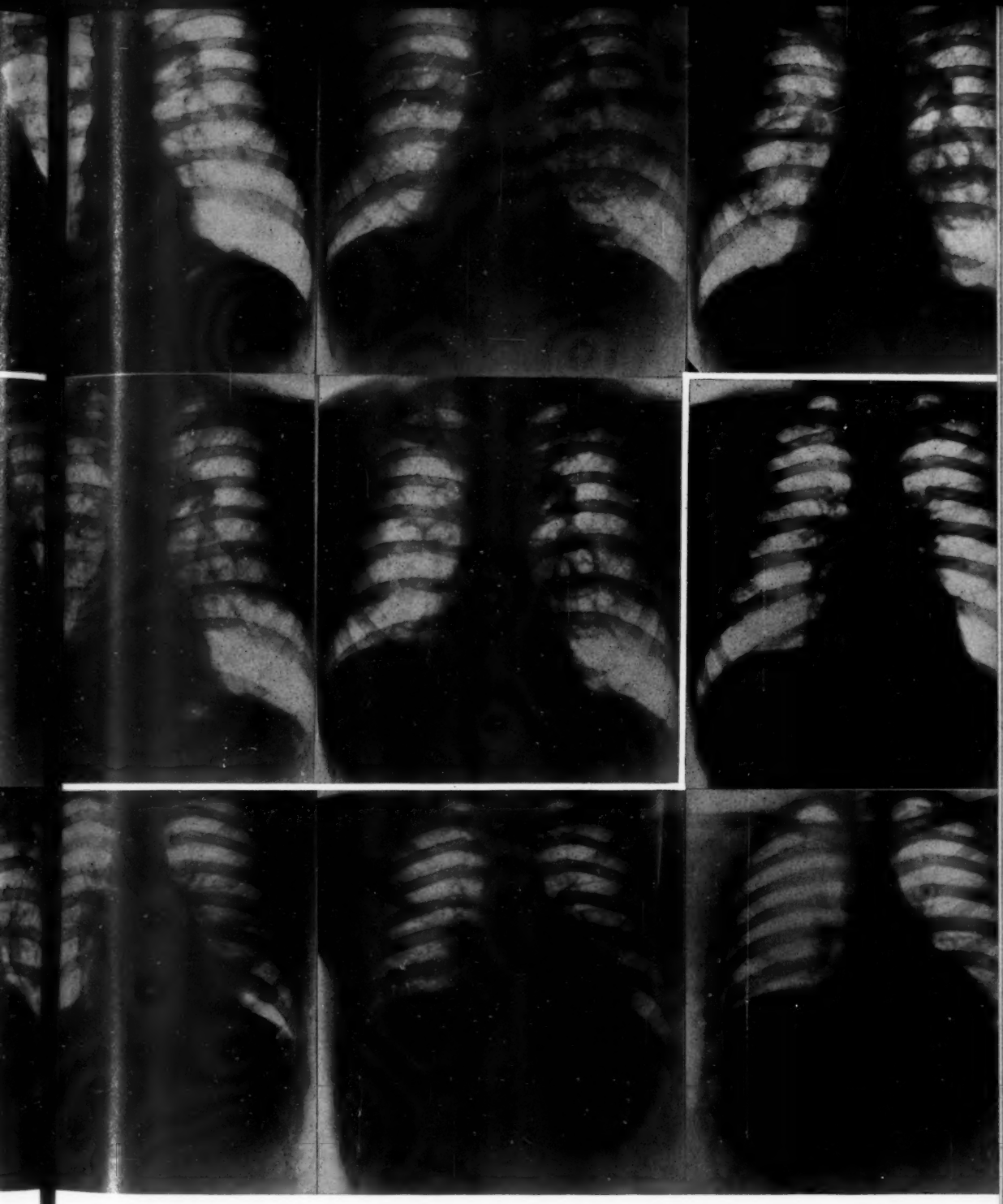

FIG. 19 FIG. 20 FIG. 21
FIG. 22 FIG. 23 FIG. 24
FIG. 25 FIG. 26 FIG. 27

PLATE 3

FIG. 19. Case 5 (a). J. S. May 14, 1931.
FIG. 20. Case 5 (b). J. S. November 14, 1932.
FIG. 21. Case 5 (c). J. S. March 16, 1933.
FIG. 22. Case 5 (d). J. S. April 27, 1933.
FIG. 23. Case 5 (e). J. S. August 24, 1933.
FIG. 24. Case 6 (a). A. H. October 15, 1932.
FIG. 25. Case 6 (b). A. H. April 3, 1933.
FIG. 26. Case 6 (c). A. H. April 28, 1933.
FIG. 27. Case 6 (d). A. H. June 12, 1933.

months later, the cavity appears unchanged. Phrenicectomy performed six years eleven months after first admission, and figure 22 shows cavity one month after operation, obliterating in a concentric manner and measuring 2.5 x 1 cm. On figure 23, five months after operation, cavity replaced by scar-tissue. Expectoration has practically ceased and free from tubercle bacilli, two months after operation.

6: No. 12,847, A. H., male, aged 26 years. On admission marked toxaemia and profuse expectoration, positive for tubercle bacilli. The major lesion seemed to be located in left lung, and artificial pneumothorax was induced on left, ten days after admission (figure 24, October 15, 1932). Sputum continued positive, and on figure 25, five and a half months after admission, right lung showed a lower lobe cavity, 1.5 x 2 cm. Pneumothorax on left was discontinued and phrenicectomy performed on right. On figure 26, three days after operation, the cavity appears to be much smaller. Figure 27, one and a half months after the operation, shows disappearance of the cavity. Sputum became negative about same time, and expectoration ceased.

The 6 cases were selected from a group of 17 patients, in all of whom the cavities became completely obliterated under therapeutic paralysis of the diaphragm. There were seven right-sided and ten left-sided cavities; thirteen of them were situated in the upper lobe and four in the lower lobe. Their sizes ranged from 1.5 x 2 cm. to 5 x 6 cm. The lowest rise of the paralyzed diaphragm after complete closure of the cavity was 1.5 cm., the highest 6.2 cm. Prior to the therapeutic interruption of the phrenic nerve all 17 patients had been placed on routine rest-cure for variable periods of time. None of the cavities showed obliterative tendencies under expectant treatment, while some of them became measurably enlarged. The 17 cases constitute 25 per cent of our tuberculous cavernous cases treated by phrenic-nerve interruption alone. In three-fourths of the cases the cavities either remained manifestly open or else their closure could not be proved roentgenographically.

Cavities extending to the visceral pleura and those situated within large diseased areas are not influenced by phrenic-nerve interruption.

Subpleural cavities generally become diffusely adherent to the chest-wall. They are immobilized and do not participate in the respiratory movements of the lung. Their walls grow thick and rigid, being unable to retract. Such cavities obviously do not share in the relaxation brought about by paralysis of the diaphragm.

Cavities situated within extensive caseopneumonic lesions are still in

the process of formation. They have no limiting walls of organized tissue and are the seat of continued destruction. Their failure to develop a fibrous capsule is due to lack of reparative processes. Mechanical obliteration of such cavities can be accomplished only through intensive compression by artificial pneumothorax. Moth-eaten cavities frequently coalesce under induced paralysis of the diaphargm, and form large excavations.

SUMMARY

Therapeutic paralysis of the diaphragm produces obliterative changes in pulmonary tuberculous cavities partly through compression, but mainly through concentric retraction of the relaxed cavity capsule. Only those cavities are influenced by phrenic-nerve interruption, the walls of which are compressible and capable of fibrotic retraction. Complete closure of responsive cavities depends on their size and on the condition of the opposite lung, and is not controlled by the amount of elevation of the paralyzed diaphragm. Cavities situated in the lower lobe show more initial compression and obliterate more rapidly than upper-lobe cavities. As an aid in closure of pulmonary tuberculous cavities phrenic paralysis presents the least radical procedure, and its application in selected cases saves the patient the inconvenience of prolonged pneumothorax treatment, the risk of major surgical-collapse operations, and the uncertainty of protracted expectant therapy.

A REVIEW OF THE CREAM-EGG CULTURE MEDIUM FOR TUBERCLE BACILLI[1]

HENRY C. SWEANY, MAX EVANOFF AND ALVIN GROSS

After many years of culturing tubercle bacilli on a cream-egg medium (1), we feel that we should bring our experiences down to date, for the benefit of those who have used or care to use the method for diagnostic culture work. We have noted with concern that many have had difficulty in making the medium according to our formula. Feldman (2) has reported difficulty, and has proposed a change that has facilitated the procedure but may have decreased the quality of the product. It is not necessary now to follow Feldman's suggestion, for a simple change in technique (to be described later) has obviated the necessity of it. Another important factor is apparently the type of inspissator and means of inspissation that have recently been adapted for general use by Sweany and Gross (3). Another suggested criticism has been that our experimental work has been performed on an insufficient number of specimens, but this objection is more apparent than real. We maintain that any method, that will only grow cultures from specimens positive by direct examination, is of little use as a diagnostic agent. *For many years our method has rarely ever failed to obtain positive cultures on positive specimens from human material.* We have, therefore, attempted to confine our crucial studies to material negative on direct examination. Recently such work has been done on sputa that were always negative or were negative for months and years by the most exacting concentration method in common use,—a method by which Sweany and Stadnichenko (4) were able to find 15 per cent more positives than by the Uhlenhuth antiformin method.

In addition, it has also been found that there are many minor details in technique of planting, which we formerly felt were obvious and needed no mention, yet which have caused some confusion.

On the whole, the process is relatively simple and may be carried out by any good laboratory staff. There is no magic about either the me-

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

dium or the method of preparation. All the ingredients of the culture medium, with the exception of the cream, have been used before, and there certainly is nothing new in the alkali or acid used for treatment of the specimens. We have, however, developed a system that has produced better results in our hands than any other for the diagnosis of all types of tubercle bacilli.

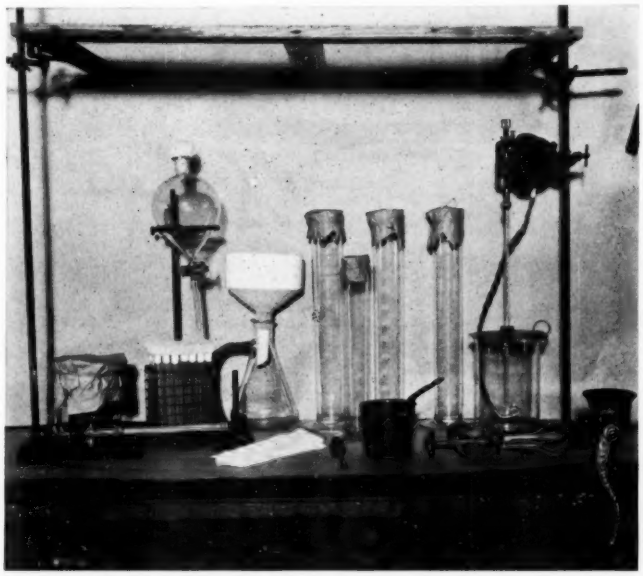

FIG. 1. Necessary equipment for the making of the medium. The various pieces are obvious to laboratory workers with the possible exception of the stirring device on the right, consisting of a motor, rod and covered beaker.

The chief reasons for success, we feel, are careful preparation and systematic procedure, with the idea ever in mind that the tubercle bacillus must be well fed and is not indifferent to even the mildest of chemicals used for the destruction or inhibition of secondary microörganisms.

THE PREPARATION OF THE MEDIUM

As nearly an aseptic technique as possible should be used. Sterile gloves are recommended where the hands come in contact with the material, and all operations should be shielded from dust. The steps are as follows:

Milk and Cream Sterilization

Sterilize 350 cc. of fresh milk and 150 cc. of fresh cream separately in an Arnold sterilizer on two successive days, for 45 minutes each. The second sterilization may be made just previous to use and the milk then added to the meat to raise the temperature more quickly.

Meat

Grind 500 gm. of fresh lean veal round steak in a sterile meat-grinder, after the whole superficial layer has been "peeled" off with a long sharp knife, using care to shield the inner part from dust and other gross contamination.

Addition of Milk

Add 350 cc. of sterilized milk, mix thoroughly, and warm up gradually to 70°C., carefully stirring to keep the temperature equal throughout.

Filtering

Place the material on several layers of sterile cheese-cloth in a 6-inch Buchner funnel, and cover with another piece of cheese-cloth. Attach to a vacuum pump, and filter.

Addition of Cream

To 350 cc. of the filtrate (there should be about this amount of filtrate) add 150 cc. of sterile cream.

Addition of Eggs

The eggs should be washed and, with shells intact, sterilized in 70 per cent alcohol for one hour; then broken carefully, beaten slowly, and filtered through gauze into a sterile cylinder to remove the froth. The milk-cream-infusion is then added to 1000 cc. of beaten eggs and the whole mixture is placed in sterile 2-litre beakers and agitated with an electric stirrer for 15 minutes. (See figure 1.) Filter twice through the same gauze into cylinders. The mixture should then be tubed from a shielded separatory funnel and immediately inspissated.

Inspissation

After slanting the tubes at the proper angle in an inspissator, the steam is turned on and the temperature raised slowly to from 82°C. to 85°C.; then shut off and allowed to cool without interference. The tempera-

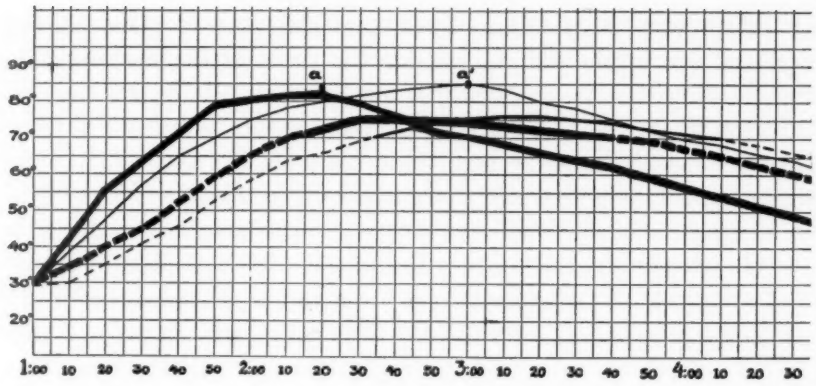

CHART 1. The first experiment is indicated by the heavy lines, the second by the thin lines; the solid lines represent the temperature in the chamber, the broken lines in the tubes of medium.

TABLE 1

The temperature changes in the inspissator and inside the tubes during inspissation (room temperature 25°C.)

TIME OF DAY	TEMPERATURE IN CHAMBER	TEMPERATURE IN TUBE
p.m.	°C.	°C.
1:00	27	28
1:10	38	30
1:20	48	35
1:30	57	42
1:40	65	47
1:50	70	53
2:00	75	58
2:10	78	63
2:20	80	66
2:30	82	69
2:40	83.5	72
2:50	84	73
3:00	85*	75
3:10	83	76
3:20	80	76
3:30	78	75
3:40	75	74
3:50	73	73
4:00	70	71
4:10	68.5	70
4:20	66	68
4:30	64	66
4:40	61	64
4:50	59	62
5:00	56	60.5

* Steam turned off.

ture curves were standardized by several experiments with two thermometers, one inside and one outside the tubes of the medium. The temperature within the medium rose more slowly and under the existing conditions was 8° to 15° lower than the temperature within the chamber. (Chart 1.) As the chart will show, the medium reaches about 73°C.–76°C. temperature, staying above 70°C. for about one hour and a half. The rise should remain somewhere between the two curves shown in the chart, that is, within ten minutes the temperature should rise somewhere between 7 and 11 degrees, or approximately 1° a minute. The medium is now adequately coagulated and will have a smooth even surface. A more accurate procedure is to raise the temperature to 82°C., then turn off twenty minutes, and again raise to 82°C. and turn off a second time. This keeps the medium between 69° and 72°C. for the required period.

Testing for Contamination

After inspissation the medium is incubated over night in a horizontal position, with a slant faced upward to dry the surface of the medium and test for contamination. The tubes are then capped with cellophane and stored in an ice-box for use. The medium must not be used after the surface shows any shrinking or any free butter fat.

THE TECHNIQUE OF CULTURING FOR TUBERCLE BACILLI

Sputum

1: Place 1 to 5 cc. of sputum into a centrifuge-tube and add an equal amount of 3 per cent NaOH. (Example: 4 cc. of sputum and add 4 cc. of 3 per cent NaOH.)

2: With a sterile pipette thoroughly mix the sputum and the NaOH. Cover up the centrifuge-tube with tinfoil or cotton plug, and incubate for 25 to 28 minutes.

3: After incubation put enough HCl (half-diluted concentrated HCl) to make the solution slightly acid. Use about 7 to 9 drops for 4 cc. of 3 per cent NaOH. The end-point is readily seen by an increase in turbidity.

4: Centrifugate at about 3000 r.p.m. for ten minutes.

5: Pour off the liquid.

6: Put into the sediment about 1.5 to 2 cc. of slightly alkaline or neutral bouillon, using a 2-cc. nipple on a Pasteur pipette, and mix thoroughly.

7: Inoculate all the material on 6 to 8 tubes of medium, using about 0.3 cc. on each.

8: Seal the tubes with paraffin by dipping the cotton plug quickly in melted paraffin, *but do not seal too tightly.*

9: Incubate at 37°C. in a moist, dark incubator.

10: After a week's time the tubes should be opened and a smear made by scraping the surface with a platinum loop. This manoeuvre does three things: it permits of a rapid stain for acid-fast bacilli in microscopic colonies or before colony-formation is visible; it reseeds small isolated colonies; and it allows fresh oxygen to enter the tube.

The same technique may be used for any contaminated material, such as urine, pus, pleural fluid, and tissue, providing there is preliminary maceration when this is necessary. With sterile material it is preferable to inoculate directly without any treatment at all.

By this method 40 to 50 specimens of sputum may be cultured in 6 to 7 hours by one worker, and a presumptive diagnosis frequently may be made in seven days, within twenty days on the average, and nearly always by thirty days.

Urine

1: Take about 100 cc. of bladder urine, catheterized, or fresh morning urine, centrifugate at high speed for 10 to 15 minutes, and pour off the supernatant urine.

2: To the sediment add any amount of salt solution and the same amount of 3 per cent NaOH. Cover up with tinfoil and incubate for 25 minutes.

3: Continue as for sputum.

Pleural Fluid, Pus and Spinal-Fluid

Inoculate with a pipette about 6 tubes of cream media, seal with paraffin, and put into incubator. Examine after 24 hours to see if any growth appears. If it is uncontaminated, nothing more need be done. If a few colonies of contamination appear, the sediment may be scraped from the uncontaminated part of the tube and replanted on other medium. Slight contamination may be diluted out by serial dilution from one tube to another, placing less and less on each subsequent tube. If it is badly contaminated it must be treated as sputum.

Tissues

The tissue should be macerated in a mortar dish, suspended in salt solution, filtered through cotton, after which follow the preceding technique.

Faeces

The same procedure as for sputum, except that the exposure to the chemical must be 45 minutes. With faeces and material contaminated with spore-forming bacteria, contaminations are common and in such material guinea-pig inoculation may be imperative.

Some types of tubercle bacilli are more sensitive to alkaline treatment than to acid for no reason known to us. Sometimes we obtain better results with 3 per cent HCl, 6 per cent H_2SO_4, or oxalic acid, than with the 3 per cent sodium hydroxide, but for routine work we prefer to use the latter. We mention the fact because there are differences in the reactibility of different strains of tubercle bacilli.

Citric acid, as recommended by Herrold (5), is also a good method for treatment, but gives a high percentage of contamination, especially with moulds. It is good for treatment before animal inoculation, because most of the virulent microörganisms are killed but the tubercle bacilli are little affected. This difference in behavior shows that even with the best of treatment there are certain times that all the tubercle bacilli will be killed. In a former report (6) this was well borne out when the treated samples were all killed, but direct planting produced luxuriant growth. After one week, if no colonies can be seen, a smear may be made by scraping the surface of the medium. Frequently numerous tubercle bacilli may be seen in this manner and the diagnosis made much earlier than waiting till the colonies appear. This has another advantage, as pointed out by Blacklock (7), in scattering the few small colonies over the medium and permitting a more abundant growth.

As a test of the method, we have listed in table 2 the sputum records of 12 patients who were always negative by direct smear but who were found positive on culture. Thirty-four more were positive only once by concentration and a large number twice, three or four times, yet were found positive on culture.

We have collected the findings for a period of two years of all specimens that were negative by the direct smear-concentration method adapted

in this laboratory, and have arranged the figures in table 3. Of 871 specimens of pus from cold abscesses, pleural and spinal fluid that were

TABLE 2

Patients who were never positive by direct examination but were positive on culture

	1930								1931												1932					
	May	June	July	August	September	October	November	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May	June
9 Conc*.....			−	−	−	−	−	−	−	−	−	−	−													
Cult.....					+					+																
23 Conc.....				−	−	−	−	−	−	−	−	−	−	−	−	−	−		−								
Cult.....											+															
30 Conc.....	−	−	−	−	−	−	−	−	−	−	−	−	−													
Cult.....						+																				
38 Conc.....	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−											
Cult.....											+															
42 Conc.....														−	−	−	−	−	−	−	−	−	−	−	−	
Cult.....																					+					
52 Conc.....																			−	−	−	−	−			
Cult.....																						+				
55 Conc.....																					−	−	−	−		
Cult.....																							+			
58 Conc.....																−	−	−	−	−	−	−	−	−		
Cult.....																					+					
63 Conc.....												−	−	−	−	−	−	−	−	−						
Cult.....																	+									
64 Conc.....															−	−	−	−	−	−	−	−				
Cult.....																					+					
67 Conc.....																			−	−	−	−				
Cult.....																					+					
68 Conc.....														−	−	−	−	−	−	−	−	−	−			
Cult.....																						+				

* Conc. = concentration method.
Cult. = culture method.

negative on direct smear, 58 were found positive on culture,—a gain of 66.7 per cent.

From 612 negative sputa, 69, or 11 per cent, were positive on cream media. Six of 214, or 2.85 per cent, were positive on culture but negative on guinea-pig inoculation. Five, or 2.33 per cent, were negative on culture but positive on guinea-pig test.

TABLE 3

The results of 612 sputum examinations that were negative by the concentration method for six months and more

	CULTURE	GUINEA PIG
354	−	
44	+	
184	−	−
19	+	+
6	+	−
5	−	+

TABLE 4

Pus, pleural and spinal fluids, negative by direct examination

	CULTURE	GUINEA PIG
19	−	−
8	−	
46	+	
11	+	+
2	−	+
1	+	−
87	58+	13+

The culture produced a net gain of 76.5 per cent in such negative cases.

While the identical specimens were not examined directly for acid-fast bacilli because the material was scanty, it is felt that few could have been found positive by direct examination because all had been running negative consistently.

COMMENT

The changes that have been made in the preparation of the medium are, in brief: (1) a standardization of inspissation; (2) a simplification of the extraction of the meat with milk and at the same time performing

the first heating to 70°C.; and (3) a rapid means of filtration through a Buchner funnel. By the use of two thermometers we were able to relate the temperature of the chamber in the inspissator to that in the tubes of medium. These curves were plotted on several occasions under different conditions, so that a sterilization for 1½ hours at 70°–73°C. may be assured from a reading of a thermometer in the chamber of the inspissator. An average rise after the steam is turned on should be about a degree a minute. When the temperature in the chamber reaches 82°C. we now turn off the steam for twenty minutes, and then turn it on and raise it again to 82°C. Formerly we heated once to 85°C. Either procedure is enough to coagulate completely, sterilize thoroughly, and render a good product.

The other changes and improvements are self-explanatory.

A problem that is also important concerns the question of culture versus animal inoculation. How can an animal be negative if the growth is positive? There are several possibilities. First, bacilli may have been present in the planted material and not in the inoculated material; and, second, the virulence of the bacilli may be too low to produce foci of disease in the animals except in large doses. This condition has been clearly demonstrated by Blacklock. We have many times noticed a lowered virulence for animals. In fact, one virulent bovine culture (no. 18) that we isolated in 1927 practically lost all its virulence within two years. This, however, is not the rule, but it happens occasionally. It is conceivable that it may occur in convalescent patients who are on the verge of suppressing the few remaining bacilli in their bodies. On the other hand, when the animals are positive with negative culture, bacilli may have reached the animal and not the culture; the technique may have been poor; or there may have been a faulty medium. On the other hand, there may be spontaneous or accidental tuberculosis in the animals. Unless the animal is on the best kind of diet, they will all acquire tuberculosis when in contact with other animals having the disease. The time varies from about three months to a year. It depends upon the diet, proximity to other infected animals, and time of exposure. Under good conditions it should not happen, but there is always the possibility. If the stock is known to be clean (as we have found ours to be) then the usual six weeks' time after inoculation is not long enough to permit the animals to develop accidental infection.

SUMMARY

A review of the cream-medium method of culturing the tubercle bacillus has been made. The technique has been simplified so that most of the difficulties encountered by others can be avoided. The method has once more been found equal to the animal-inoculation method in percentage recoveries of tubercle bacilli from all specimens free from certain spore-forming bacteria. Eleven per cent more positives were found on the sputum of tuberculous patients (always negative, or negative for more than six months) than were found by the direct incubation-concentration method. Although animal inoculation cannot be entirely dispensed with, the bulk of diagnoses can be made by culture, if there is a properly equipped laboratory and a technician adequately trained in the work.[2] The advantages of cultures are (1) they may be repeated more frequently; (2) they are more absolute; (3) the diagnoses on the average may be made in approximately half the time; and (4) with 6 inoculated tubes they are about 10 per cent the cost of one animal. The disadvantages are principally the difficulty in assembling the proper equipment and establishing a consistent technique.

Addendum

In a recent article, Schaffer (AMERICAN REVIEW OF TUBERCULOSIS, 1933, xxvii, 259) reports a comparison of various methods of culturing tubercle bacilli in which the "Sweany-Evanoff" method was found to be less satisfactory than certain others. It must be pointed out, however, that he used an old experimental combination, long since displaced by the cream medium (*Tubercle*, June, 1930, xi, 404). Fortunately we are able to evaluate the quality and refinement of this work by the author's conclusions that the best methods "were equal to the microscopic method in total number of positive results." We contend that a method to-day is practically useless unless it produces better results than even the best microscopic method. The fact that we can grow from practically every type of material any viable tubercle bacillus, human, avian or bovine, speaks for itself. Outside of Loewenstein's yet unconfirmed method, no other can approach this record.

[2] The Central Scientific Company of Chicago is able to supply the needed equipment for this work.

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THE INHIBITORY ACTION OF SULPHUR ON THE GROWTH OF TUBERCLE BACILLI

GEORGE B. LAWSON[1]

We have studied the effects of various concentrations of sulphur on the growth of tubercle bacilli. Corper's mashed-potato medium has been used exclusively in this study. Accurately weighed quantities of flowers of sulphur were added to each 100 cc. of medium; then the medium was autoclaved, cooled to around 45°C., thoroughly shaken, pipetted into test tubes and immediately placed on ice to maintain an even distribution of sulphur. These culture tubes were then incubated several days to ensure sterility.

To obtain a fairly uniform seeding in each culture, a saline suspension of tubercle bacilli was made and one loopful transplanted on each culture tube.

The results were as follows:

Comparison of growth of tubercle bacilli on sulphur medium and on controls

MILLIGRAMS OF SULPHUR IN EACH 100 CC. MEDIUM	TEN TUBES FROM EACH 100 CC. OF MEDIUM, SEEDED WITH TUBERCLE BACILLI	CONTROLS WITHOUT SULPHUR
400	Negative	Positive
300	Negative	Positive
200	Negative	Positive
100	Negative	Positive
80	Negative	Positive
60	Negative	Positive
50	Negative	Positive
40	Negative	Positive
30	Negative	Positive
20	Negative	Positive
10	Negative	Positive
9	Negative	Positive
8	Negative	Positive
7	Negative	Positive
6	Negative	Positive
5	Negative	Positive
4	Negative	Positive
3	Negative	Positive

(A few of the above cultures were discarded because of contaminations.)

[1] Roanoke, Virginia.

There is apparently no increase in acidity up to 30 mgm. sulphur per 100 cc. of medium, using brom-thymol-blue as indicator; however, due to the opaqueness of the medium it has been hard to determine an accurate end-point.

We have not determined whether or not this inhibitory action is due to the sulphur itself or to some compound. These experiments are tentative and suggestive of further study. We have made a few experiments with some of the ordinary pathogenic bacteria, and the sulphur seems to have no inhibitory effect on their growth.

All of the technical work in this study has been done by Mr. A. W. Bengtson, in the laboratory at Catawba Sanatorium, Catawba Sanatorium, Virginia.

A QUANTITATIVE STUDY OF THE TUBERCULIN REACTION IN CHILDHOOD TUBERCULOSIS

J. A. JOHNSTON, P. J. HOWARD AND JOHN MARONEY[1]

Allergy in tuberculosis has been studied quantitatively by a number of workers. The two methods used have been the injection of serial dilutions, the observation being made of the amount required to elicit a local reaction, and the measurement of the local reaction, the amount injected being constant. This latter is open to considerable objection technically, for, while the response to varying amounts will usually be paralleled by variations in the size of the wheal, in some instances the threshold obtained by using serial dilutions is extremely sharp, and a very large reaction with one dilution will be accompanied by no reaction at all with the next higher dilution.

The method used here was that employed in animals by Römer and Joseph (1), who showed a rising curve of sensitivity with the extension of infection, and demonstrated that the height of the curve and the rapidity with which it rose paralleled directly the intensity of the infection. Ellermann and Erlandsen (2), with a technique which combined the use of dilutions and measurement of the wheal, concluded that there was a direct relation between sensitivity and the grade of tuberculous infection and that a fall occurs with quiescence of the lesion. Baldwin (3), Krause (4), and Willis (5) have likewise studied it in animals. Krause states that allergy falls with the retrogression and healing of the tubercle and that it increases with the extension or repetition of the infection. Baldwin, Petroff and Gardner (6) state that the onset of progressive disease gives rise to a high degree of sensitiveness, which in most cases persists for years after an apparently complete arrest of the disease. Atsatt (7) and Blair and Galland (8), making a quantitative study of allergy in bone tuberculosis, felt that very high levels were attained and that below certain critical thresholds, on which, however, they did not agree, activity of the process could be excluded. Schwartz and Heise (9), in a study of the quantitative reaction among active adult-type cases, concluded that no reliable information could be ob-

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tained about extent or activity, but noticed a rise in the level of allergy with both healing and with minor relapses. Happ and Casparis (10) pointed out that the seemingly "lost" ability to react was merely a quantitative matter and that any case would react if given sufficient antigen. Dickey (11), studying the size of the reacting area, noted the high sensitivity in phlyctenular conjunctivitis, bone and lymph-node tuberculosis, and was unable to find a definite correlation between the size of the area and activity. White and Graham (12), using serial dilutions and the Pirquet technique, felt that there was a direct relationship between activity and sensitivity. Apropos the relation of allergy to immunity Willis (13) showed that in the face of a gradually declining cutaneous allergy with the subsidence of infection, his animals continued to show a high immunity.

The present study is based on observations on 213 children with first infections, discovered largely through a survey of contacts and followed in the hospital during the past two years, and of more than 500 children followed in the outpatient department as reactors over a period of six years. Serial dilutions of Old Tuberculin were given intracutaneously at monthly intervals and the "threshold" taken as the weakest dilution to which any local response was elicited. In the beginning 0.000,001 mgm. was arbitrarily chosen as the smallest amount used, but in the last six months we have used doses as small as 0.000,000,01 mgm. The tuberculin used was a single lot prepared for us by Gardner at Saranac Lake six years ago and kept undiluted until just before the tests. To avoid local sensitization, different sites were chosen for testing each month. A possible theoretical objection to the technique employed is that it is known that sensitivity can be heightened by repeated injections. The use of a monthly interval for testing may render this less likely, but it still remains a possibility in the explanation of our curves. Against it is the fact that while the majority show a rise and fall, some start high and decline. Three or four intracutaneous tests were applied simultaneously, the doses likely to give an end-point being estimated from experience. When all tests were positive or all negative, a blank is recorded in the protocols and a month was allowed to elapse before re-testing. Studies of the blood paralleled the tuberculins and X-ray films were taken at intervals of two months.

Our findings were as follows: If the pulmonary phase of the first infection be divided for convenience into three stages, the following three X-ray plates could be classed as representative of each: (1) the

plate showing the exudation of infiltration in the parenchyma of the lung; (2) the plate showing the parenchyma relatively clear but the hilum region enlarged; (3) the hilum nodes diminished in size and showing calcification. While it was never possible definitely to date the age of the first plate, the series of events is quite well established and is known to occupy about two years. X-ray plates show the stages of the process. In the first plate is seen a diffuse even shadow occupying the right lower lobe. In the second plate this shadow is seen to have diminished in size, and in the third plate calcium is evident in this primary focus.

There is omitted from this communication any consideration of secondary lesions. The allergic situation in these is extremely complicated and, while we have observations on the adult type of pulmonary lesion and on bone lesions, we are not yet prepared to offer a satisfactory interpretation of them.

Changes in the blood are quantitatively not as great as have been reported in secondary tuberculous infections but parallel these; in general, the findings were as follows: The total count was usually normal, there was a steady decline in polymorphonuclear cells and a rise in lymphocytes together with a fall in monocytes. The most consistent finding, however, was the definite shift to the left in the Arneth index with a gradual move to the right with the involution of the process. In the protocols the Arneth index is the ratio of the number of early or immature polymorphonuclear cells to the number of mature cells. As these patients were all children whose total polymorphonuclear count is normally lower than in adult life the indices may seem to be unusually low. Considerable normal variation must be allowed for, but we feel that indices below 1:10 are definitely in the zone of activity.

The course of the tuberculin threshold was as follows: There was a steady rise over a period of from three to eight months throughout stage 1, the maintenance of a high plateau for an additional period of several months, and then a gradual fall. The highest point seemed to coincide more or less with a maximum involvement of lymph nodes. No patients in the hospitalized group have been followed long enough to observe a complete disappearance of reactivity. Among the reactors followed for six years, however, we have observed reactions become negative to 1 mgm. in 13 instances. In only one of these, however, have we found a chest plate positive for evidence of the childhood lesion.

COMMENT

The relationship we have attempted to establish in the initial pulmonary infection might be thought of in terms of time or related to the anatomical pathological changes; that the latter must influence it very greatly is suggested by the well-established high threshold in bone and lymph-node lesions. The most reasonable interpretation appears to us to be that the maximum level of sensitivity corresponds with maximal involvement of lymph nodes, quite low levels being found early in the infection when the plate shows rather massive involvement of the parenchyma, the titre rising with a clearing of the parenchyma and an enlargement of the lymph nodes, declining again as the nodes diminish in size and calcify. The presence of a stage of some months' duration at the beginning of the infection as well as toward the end, when the level of allergy may be comparatively low, would render any conclusions relating activity to high titres quite unreliable. It is, incidentally, the stage of steady increase in titre corresponding, not with extension of the process, but with absorption of the parenchymal lesion, that would seem to be at variance with the findings of other workers.

Even in many instances in which the rising and falling tuberculin curve is observed and the blood picture suggests steady healing there is apparent no constant time relationship between the two phenomena. Thus, the tuberculin curve has been seen to rise to its peak, fall, and be maintained at a fairly low level, and this curve noted to accompany clearing of the parenchymal shadow in the X-ray, and yet for a long period afterward (a year or more) the blood picture will reflect activity. And, conversely, extremely high sensitivity thresholds have been seen to be maintained for many months when the blood picture was quite normal.

The discordant results in the use of tuberculin in phlyctenular conjunctivitis might easily be explained by a failure to ascertain the threshold at which the attempt to desensitize was being started and the use of an arbitrary set of dilutions for all cases.

It would be outside the scope of this paper to relate these data to the problem of immunity but the following more or less accidental observation should be recorded. No one considers as unusual the absorption of massive exudates of the first infection; it is not a usual experience, however, to see healing in the disseminated type. The series of over 200 hospital cases includes five disseminated types and one miliary case which

recovered. In all of these a fatal prognosis had been given on admission. We are wondering whether the monthly administration of the tuberculin in doses at or near the threshold of reactivity, in conjunction with hygienic measures which included large doses of codliver oil and light, may have had something of the effect that was described by de Savitsch, Trevorrow, Black and Lewis (14). These workers found that calcifying agents were ineffectual when used alone, as were injections of tuberculin, but the authors noted a striking therapeutic effect from a combination of the two.

SUMMARY

The reaction to tuberculin in the childhood type of tuberculosis has been studied throughout the evolution of the primary complex and found to follow a curve which rose to a high peak following the absorption of the parenchymal lesion and corresponding with the maximal involvement of the hilum lymph nodes, and then to decline with the diminution in size of these nodes and their calcification. While this course of events is usually paralleled by peripheral blood changes associated with healing, the same tuberculin course was seen when X-rays showed absorption but the blood picture remained equivocal, or even showed retrogression. It is our feeling that these data favor the concept that the allergic and immune phenomena, in so far as the latter are reflected in the peripheral blood, are relatively independent.

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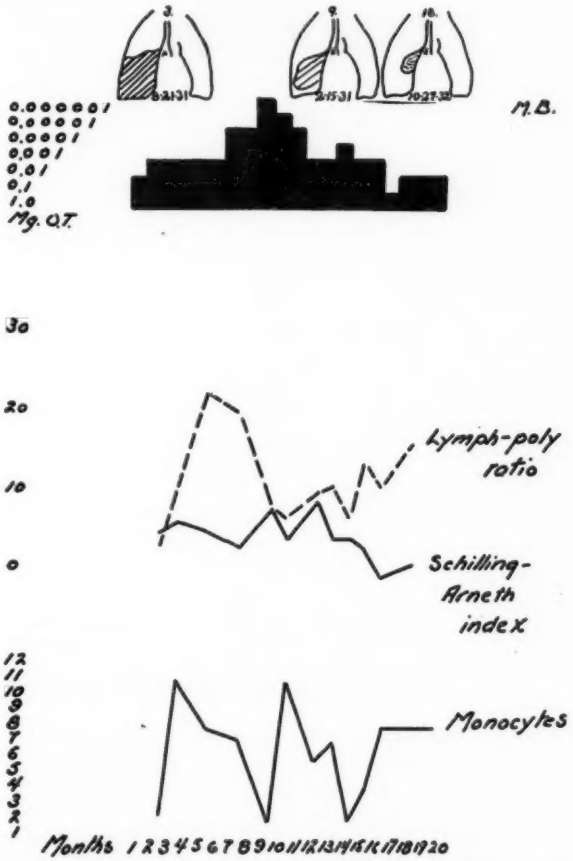

CHART 1. (M. B.) The initial level of sensitivity (0.01 mgm.) is found to correspond with an X-ray plate showing a diffuse shadow involving the entire right lower lobe. The blood is characteristic of active infection. The highest point of sensitivity is reached in the ninth month and corresponds with a plate which shows that considerable absorption has taken place. A low level is again attained in the seventeenth month, at which time the X-ray shows that the parenchymal shadow has been largely absorbed and calcium has appeared in the hilum lymph nodes. The blood continues to show marked evidence of activity: lymphocytes low relative to the polymorphonuclear cells, and these showing an abnormally large percentage of immature forms.

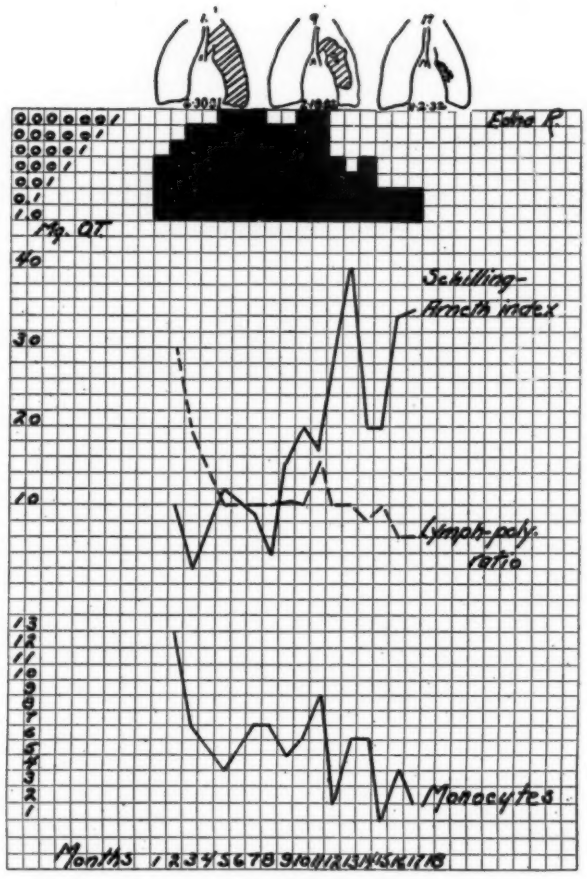

CHART 2. (Edna R.) High level of sensitivity reached in the fifth month. The parenchymal shadow has definitely diminished in size. Evidences of activity in the blood have declined, as judged by the rise in lymphocytes and the fall in polymorphonuclear cells, but the Arneth index does not start to rise into the normal zone until about the tenth month. At this time sensitivity is still at a high point (0.000,001 mgm., the highest dilution used in this case). It has fallen to 0.01 mgm. by the fifteenth month, at which time calcium is evident in the X-ray.

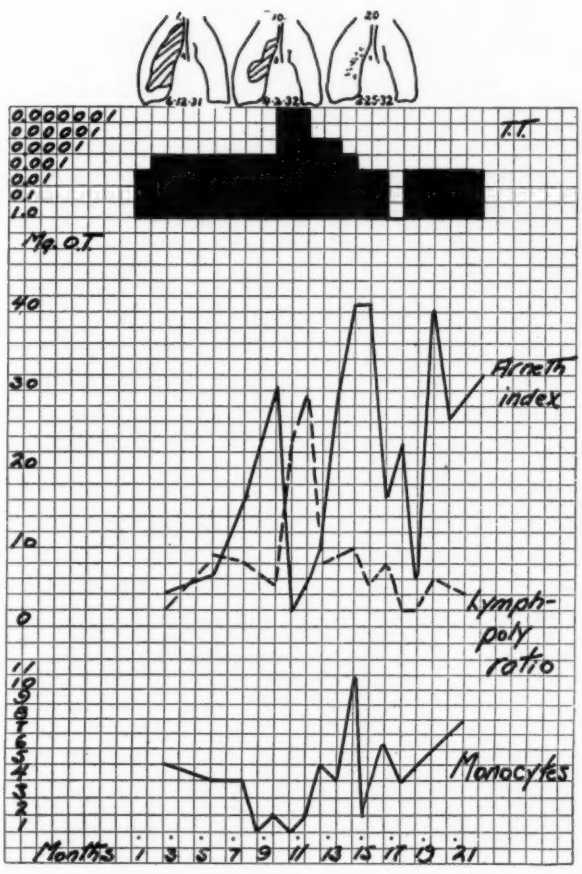

CHART 3. (T. T.) The level of sensitivity rises to a peak in 10 months and then declines. The course of the blood picture in general is one of improvement. Frequent breaks in the curve, as well as a complete loss of reactivity in the 17th month, are probably explained by intercurrent infections; the child had numerous attacks of tonsillitis and otitis media. The high point in the sensitivity curve corresponds with an X-ray plate which shows that considerable absorption has taken place.

THE DESENSITIZATION OF TUBERCULOUS GUINEA PIGS BY MEANS OF NATURAL TUBERCULIN PREPARED FROM FRACTURED BACILLI

JOHN WEINZIRL AND RUSSELL S. WEISER[1]

Desensitization in tuberculosis is a special line of investigation which has been pursued in this laboratory for some time. This work has led to the employment of a large number of antigens prepared from the tubercle bacillus by diverse methods in an endeavor to secure one highly efficient for a desensitization treatment of tuberculosis. Previously, *Synthetic-Medium Tuberculin* has been found capable of desensitizing tuberculous guinea pigs against a lethal dose of tuberculin. To this we now add another which we designate *Natural Tuberculin* because it consists of the inner contents of the tubercle bacillus, liberated by fracturing the organism, and because it has not been changed by chemicals or by heat.

The benefits to the tuberculous animal, which we believe will result from desensitization, have been emphasized in previous papers (1) (2). Briefly, we believe that necrosis and progression of the tubercle are the results of allergic reactions in highly sensitized cells about the tubercle; that this same reaction in the more or less allergic cells of the various tissues of the body may impair their normal function, and may interfere with the development and operation of immune mechanisms.

Wherry (3), 1931, suggested that allergic destruction of tissue may supply substances upon which organisms flourish, and which may also dilute the antibodies present. This would appear to be true in tuberculosis, since tubercle bacilli flourish more readily in animals made allergic with tuberculoprotein than in nonallergic animals. Austrian (4), 1913, found that tuberculin-sensitized guinea pigs and rabbits were less resistant to tuberculosis than were controls. This is in harmony with the views of Stewart (5), 1933, and Myers (6), 1933, who believe that the destructive form of tuberculosis after puberty develops in the "allergic soil" of childhood infection. Lurie (7), 1933, found that the tubercle bacillus grows rapidly and unhindered in the necrotic area of the tubercle.

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In these areas the invading mononuclears and polymorphonuclears undergo necrosis as a result of the allergic reaction. They are thus made ineffective in combating the bacilli; hence the tubercle continues to progress and finally ruptures with the liberation of large numbers of bacilli. Lurie's work indicates that mononuclear phagocytes are the chief agents of immunity in tuberculosis, that the greatest immunity is associated with *in situ* mononuclear phagocytosis in the various organs, and that the enhanced avidity of the mononuclear phagocyte in the immune animal often permits the destruction of bacilli of reinfection without the formation of a lesion. Such evidence tends to discount the alleged importance of allergy as a defense mechanism; on the contrary, it indicates that the allergic reaction may serve to disarm the phagocytes and prevent their destroying the bacilli, thus strengthening the argument in favor of desensitization.

Previous investigations in this laboratory have shown that relatively undenatured antigens are the most successful for the desensitization of tuberculous guinea pigs. For this reason we have sought to employ methods which involve as little denaturation of the antigen as possible. Nelson (8), 1926, succeeded in securing very specific intracellular globulins from organisms of the colon-typhoid group by means of repeated freezing with liquid air followed by electrodialysis. This work suggested to us the possibility of preparing a natural tuberculin which might prove highly specific, since it would involve little or no denaturation of the proteins contained in the bacilli, and it might provide an antigen more effective for desensitization than the older tuberculins.

METHODS EMPLOYED

Preparation of antigen: The antigens were prepared from cultures of tubercle bacilli grown four to five weeks on Long's synthetic medium. The cultures employed were the virulent strain, H37, and the relatively avirulent strain, H178. Masses of the bacilli were removed from the substrate and gently ground in a mortar to secure subdivision of the clumped organisms. The bacilli were then washed in physiological saline solution in order to remove as much of the medium and metabolic products as possible. This was accomplished by centrifugating several times in 8- to 10-volume portions of the saline solution. A heavy suspension of the organisms was transferred to tubes and subjected to freezing with liquid air according to the method employed by Nelson (3); this process ruptured the cell walls, and liberated the cell contents which were used as an antigen. Freezing by means of solid carbon-dioxide was also attempted, but this method proved less efficient than liquid air and it

was finally abandoned. After thirty-five consecutive freezings the material was centrifugated and the clear supernatant fluid obtained was used for desensitization work without further treatment. It gave the usual tests for proteins and carbohydrates and yielded a precipitate upon the addition of trichloracetic acid amounting to 10 mgm. per cc.; the total solids amounted to 19.1 mgm. per cubic centimetre. Inoculation of the antigen on suitable media gave no growth, and, when injected into guinea pigs, it failed to produce infection. The antigen proved to be highly potent for the systemic testing of tuberculous guinea pigs; a dose as low as 0.7 mgm. frequently being fatal to highly sensitized tuberculous guinea pigs of 300-gm. weight. The antigen was sealed in tubes and preserved by freezing at −10°C. until used. It is referred to in this paper as *Natural Tuberculin*, or *N. T.*

Animal experiments: Guinea pigs were infected with tubercle bacilli, strains H178 and H37, the former being low in virulence, the latter relatively high. Desensitization was begun as soon as the animals became sensitive, as determined by the skin test, which was usually about a month following infection. The dosage of antigen and the route of administration were varied in the different protocols.

EXPERIMENTAL RESULTS

Protocol 1: Guinea pigs were infected intraperitoneally with 0.3 mgm. tubercle bacilli, H178, an organism of low virulence. The first desensitizing dose of Natural Tuberculin was given intraperitoneally on the 49th day after infection. Treatment was continued weekly for nine weeks, when the systemic test was given; a dose of 0.8 mgm. of Seibert's S.M.T. was injected intraperitoneally on the 115th day following infection, to determine whether desensitization had been accomplished.

PROTOCOL 1

Desensitization of tuberculous guinea pigs by means of Natural Tuberculin prepared from fractured tubercle bacilli

	UNIT	DAY	TREATED ANIMALS	TUBERCULOUS CONTROLS
Animals	No.		5	4
Average weight	Gm.	1	406	375
Living H178	Mgm.	1	0.3	0.3
Antigen, N.T.	Mgm.	49	0.8	0
Doses	No.		10	0
Average weight	Gm.	116	509	415
Systemic test, S.M.T.	Mgm.	115	0.8	0.8
Tested	No.	115	5	4
Survived	No.	116	5	0
Percent survived			100	0

The treated animals survived the systemic test, whereas all of the controls died within eighteen to thirty-six hours. Within two hours after the test dose was given, the difference between control and treated animals was very marked; the former showed severe shock while the latter exhibited only slight symptoms.

Protocol 2: Guinea pigs were infected in the same manner as in protocol 1. Treatment was begun on the 36th day. The test animals were divided into three groups: one received the Natural Tuberculin; a second, well-washed cell debris obtained from freezing the bacilli; and the third, cell debris plus the Natural Tuberculin. This protocol was intended to confirm the first, and to determine whether or not the cell debris possesses desensitizing powers. The antigens used in this protocol were given intraperitoneally at semi-weekly intervals.

PROTOCOL 2

Desensitization of tuberculous guinea pigs by means of Natural Tuberculin and insoluble débris

	UNIT	DAY	ANIMALS TREATED WITH:			TUBERCULOUS CONTROLS
			N.T.	N.T. and débris	Débris	
Animals	No.		4	4	4	8
Average weight	Gm.	1	314	333	324	304
Living H178	Mgm.	1	0.3	0.3	0.3	0.3
Antigen	Mgm.	36	0.1	1.1	1.0	0
Doses	No.		10.0	10.0	10.0	0
Average weight	Gm.	77	415	398	394	479
Systemic test, N.T.	Mgm.	77	5.0	5.0	5.0	5.0
Tested	No.	77	4	2	3	6
Survived	No.	78	4	2	0	0
Percent survived			100	100	0	0

In protocol 2 the Natural Tuberculin was used for the systemic test in order to determine desensitization to the homologous antigen. The dose was 7.0 mgm., amounting to 10 M.L.D. for a 300-gram guinea pig giving a 4+ skin reaction. The animals of the group receiving the Natural Tuberculin, and, of the group receiving the cell debris plus Natural Tuberculin, all survived the systemic test given on the 77th day; the controls and the treated animals receiving only cell debris, all died within 4 to 7 hours. This would indicate that the cell debris possessed little, if any, desensitizing powers. All the animals receiving cell debris

showed adhesions in the peritoneum, and their physical condition was poor as compared with the other animals of the protocol; several died of intercurrent infections during the process of treatment. This protocol confirmed the results obtained in the first, and it showed complete desensitization to the homologous antigen.

Protocol 3: This protocol was carried out, using 1.0 mgm. tubercle bacilli, H178, a larger infecting dose. Sensitivity developed early in the guinea pigs, and treatment was begun on the 25th day. The treated animals were divided into two groups. Natural Tuberculin was administered intramuscularly to one group, and subcutaneously to the other. The purpose of this protocol was to determine the effectiveness of desensitization by these two routes.

PROTOCOL 3

Desensitization of tuberculous guinea pigs by means of Natural Tuberculin

	UNIT	DAY	ANIMALS TREATED:		TUBERCULOUS CONTROLS
			Subcutaneously	Intramuscularly	
Animals	No.		4	4	4
Average weight	Gm.	1	370	342	350
Living H178	Mgm.	1	1.0	1.0	1.0
Antigen, N.T.	Mgm.	25	0.07	0.07	0
Doses	No.		11	11	0
Average weight	Gm.	105	566	527	535
Systemic test, S.M.T.	Mgm.	105	3.0	3.0	3.0
Tested	No.	105	4	4	4
Survived	No.	106	3	4	0
Percent survived			75	100	0

The systemic test caused the death of one animal treated subcutaneously, and definite signs of shock in two others. All of the controls succumbed, while all of the animals treated intramuscularly exhibited only slight signs of shock. In this protocol the intramuscular route was more effective for desensitization purposes than the subcutaneous route.

Protocol 4: An infecting dose of 0.2 mgm. tubercle bacilli, H37, was given by the intraperitoneal route; this constituted a more severe infection than that employed in the former protocols. The guinea pigs became sensitive at an early date, and treatment was begun on the 21st day. Intraperitoneal injections of the homologous Natural Tuberculin,

that is, N.T. prepared from H37, were given every other day. The initial dose was 0.07 mgm. and each dose was increased by 0.05 mgm. each successive time.

PROTOCOL 4

Desensitization of tuberculous guinea pigs by means of Natural Tuberculin in constantly increasing doses

	UNIT	DAY	TREATED ANIMALS (N.T. INCREASED 0.05 MGM. EACH TIME)	TUBERCULOUS CONTROLS
Animals	No.	1	9	9
Average weight	Gm.	1	215	218
Living H37	Mgm.	1	0.2	0.2
Antigen, N.T.	Mgm.	21	0.07	0
Doses	No.		14	0
Total antigen	Mgm.		5.53	0
Average weight	Gm.	49	327	342
Systemic test, N.T.	Mgm.	49	7	7
Tested	No.	49	7	6
Survived	No.	50	5	0
Percent survived			71.5	0

The systemic test was given on the 49th day as the animals were beginning to die from advanced tuberculosis. Two of the treated animals died following the systemic test, but these two were in a very weak condition when the test was given. The remaining treated animals showed only slight symptoms of shock, while all of the control animals died of shock. This protocol showed, therefore, that desensitization is possible even when the guinea pigs are infected with the virulent strain of tubercle bacilli, H37.

Degree of desensitization: In order to determine the completeness of desensitization in guinea pigs surviving the systemic test, a number of animals in the various protocols were given large doses of the antigen reaching as high as 60 M.L.D. without producing a lethal effect. This indicates that desensitization can be made quite complete by means of Natural Tuberculin.

The M.L.D. of the antigen for normal guinea pigs has not been definitely determined but it is undoubtedly quite high, since 50 mgm. have been given without producing death or even symptoms of shock.

DISCUSSION

The Alice McDermott Foundation has published several papers presenting the results obtained when various antigens are tested for desensitization powers in tuberculous guinea pigs. Many antigens have been tried, but only one has been found previously that will protect a tuberculous guinea pig against a Minimal Lethal Dose of tuberculin, namely, Synthetic-Medium Tuberculin, or S.M.T. This antigen consists of proteins precipitated from the synthetic medium in which the tubercle bacillus has grown. Since Old Tuberculin, O.T., contains soluble protein presumably similar to some in S.M.T., it would appear that it should be available for desensitization, but in the trials made it proved to be too toxic. In other words, it was found impossible to administer a dose sufficiently large to desensitize without killing the animals.

In the trials with bacilli killed in various ways, it has been impossible to secure an antigen that will desensitize sufficiently to protect fully against a Minimal Lethal Dose. Since the bacilli contain the proteins that produce the sensitization, it would seem that these proteins should also effectively desensitize. Apparently, these proteins are ineffectual desensitizers while encased in the cell walls of the bacilli; apparently, they must be released before they can serve as antigens, at least this has been our experience thus far; apparently, the desensitizing dose of antigen must be larger than the sensitizing dose in order to be effective.

In the present investigation, the plan has been to release the proteins of the tubercle bacilli by rupturing the cell walls in a manner similar to that of cracking the shells of eggs to release the contents. Several ways of fracturing the cells have been tried, but the method of freezing with liquid air and then thawing was found to work most satisfactorily. Approximately 35 alternate freezings and thawings were required to kill all the bacilli. The product obtained was a highly colloidal substance resembling the white of eggs in appearance. This was diluted with saline solution, centrifugated to remove the insoluble debris, and the supernate was tested for desensitizing powers. As the protocols have shown, this antigen, which we have designated as *Natural Tuberculin*, or *N.T.*, has been successfully employed to desensitize tuberculous guinea pigs even to as much as 60 M.L.D. No attempt was made to determine the limit of desensitization.

In one of the protocols the cell remains, or debris, were used as antigen to desensitize, but they failed to show any desensitizing powers for tuberculous guinea pigs. We attribute this to their relative insolubility.

Natural Tuberculin is a new product differing materially from the tuberculins previously prepared. It contains all the saline-soluble proteins of the tubercle bacillus, presumably in much the same conditions as they were formed, unaltered by chemicals or heat. It should act, therefore, similarly to proteins from living tubercle bacilli, and it should be an effective desensitizing antigen. We have found that exceedingly small doses will kill tuberculous guinea pigs, but, employed in sublethal doses, it will effectively desensitize, the animals exhibiting little or no shock after an injection.

CONCLUSIONS

1. Tuberculous guinea pigs can be desensitized by means of a natural tuberculin prepared from tubercle bacilli subjected to repeated freezings with liquid air.

2. No desensitizing powers could be demonstrated for the cell debris remaining after the removal of the natural tuberculin.

3. The natural tuberculin successfully desensitized guinea pigs infected with either nonvirulent or virulent tubercle bacilli.

4. Desensitization was effective against both Seibert's Synthetic-Medium Tuberculin, and against the homologous Natural Tuberculin.

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THE TRYPTOPHANE TEST IN TUBERCULOUS MENINGITIS[1]

MILTON B. ROSENBLATT

The difficulty of demonstrating the tubercle bacillus in the spinal fluid of patients with tuberculous meningitis, particularly in the early stages of the disease, has been responsible for attempts to devise a specific reaction which would be far less time-consuming. During the past fifteen years many types of tests have been suggested. While such procedures as the acetone test (1) and the tuberculin test (2) on the spinal fluid are now apparently obsolete, the Levinson test and the chloride test are still in use. The unfortunate feature common to all these procedures is that, while positive reactions are obtained with the spinal fluid of the tuberculous-meningitis cases, they are also obtained in other conditions. For example, Giordano and Abelson (3), in a large series of cases, found the number of "false positive" reactions with the Levinson test to be as high as 32 per cent.

The tryptophane test is another attempt at a specific reaction. It was introduced into Italy by Brugi and Aiello. The technique consists of pouring 2–3 cc. of spinal fluid into a test-tube, to which is added 15–18 cc. of concentrated hydrochloric acid and 2–3 drops of formaldehyde (2 per cent). The tube is inverted a few times and then allowed to stand for 4–5 minutes. The mixture is then layered with 1–2 cc. of sodium nitrite (0.06 per cent). In a few minutes, if the reaction is positive, a delicate violet ring forms at the junction of the two liquids. A negative reaction is characterized by either the absence of color change or the formation of a brown ring. According to Aiello, the reaction is due to the presence of free tryptophane, which has been separated from the fibrin in the spinal fluid by the action of autolytic enzymes. Brugi (4) found the test to be positive only in cases of tuberculous meningitis. Aiello (5), after reviewing a large series of cases, concluded that the reaction was positive in more than 90 per cent of all cases of tuberculous meningitis but that false reactions were obtained in 2 per cent.

[1] From the Tuberculosis Division, Montefiore Hospital, Dr. Maurice Fishberg, Chief of Division.

In this country, Lichtenberg (6) reported a series of cases from the Pediatrics Division of the Johns Hopkins Hospital. There were 25 cases of tuberculous meningitis and 53 controls. The controls included instances of encephalitis, brain abscess, the various meningitides, tetanus, intracranial haemorrhage, meningismus, and a group of tuberculosis patients erroneously suspected of meningeal complication. The spinal fluids in the tuberculous-meningitis cases all gave positive reactions. Forty of the controls gave negative reactions. Thirteen of the controls gave "false positive" reactions, which were purplish in color rather than the violet obtained in the cases of tuberculous meningitis. In these 13 cases the spinal fluids were either purulent or xanthochromic. Lichtenberg stated that haemorrhagic fluids also gave "false positive" reactions. The increase of protein in the spinal fluid was not the sole cause for the false reactions, because there were 11 cases with increased globulin which gave negative results. This point was also emphasized by Aiello.

The tryptophane test has been in use at the Montefiore Hospital for one year. During this time there were 12 cases of tuberculous meningitis proved by autopsy or demonstration of the tubercle bacillus in the spinal fluid. All of these cases gave unquestionably positive reactions. The control group comprised 45 cases which have been arranged in three divisions for analysis.

1: Pulmonary Tuberculosis Patients Erroneously Suspected of Having Meningeal Involvement

Number of cases: 18
Spinal fluid: all negative
Tryptophane test: all negative

2: Nontuberculosis Patients

Disease	*No. of cases*
Pernicious anaemia	2
Uraemia	1
Spinal-cord tumor	1
Cerebral arteriosclerosis	4
Postencephalitis	1
Intramedullary cord disease	2
Birth trauma	1
Carcinoma of pancreas	1
Multiple sclerosis	1
Pituitary disease	1

Disease	*No. of cases*
Hypertensive encephalopathy	2

Number of cases: 17
Spinal fluid: all negative
Tryptophane test: all negative

3: Nontuberculosis Patients

Disease	*No. of cases*	*Tryptophane*
Cerebral haemorrhage	1	negative
Traumatic myelopathy	1	negative
Syringomyelia	1	negative
Streptococcus meningitis	1	negative
Intramedullary cord disease	1	negative
Tabes	1	negative
Von Recklinghausen's disease (xanthochromic fluid)	1	positive
C. N. S. syphilis	1	positive
Hypertensive encephalopathy	1	positive
Obstructive jaundice (bile-tinged fluid)	1	positive

Number of cases: 10
Spinal fluid: all abnormal (increased protein, pleocytosis, etc.)
Tryptophane test: four cases positive

Of the four "false positive" reactions only the xanthochromic fluid gave a purplish color ring. Our observations confirmed those of Lichtenberg with respect to haemorrhagic fluids. If the fluid was grossly haemorrhagic, a purplish ring was invariably obtained. The presence of a few red-blood cells, however, did not affect the reaction. Lichtenberg found that fluids containing up to 400 red-blood cells per cubic millimetre did not give false reactions. In our work, fluids were encountered containing as many as 2,000 cells without giving "false positive" reactions. In the cases in the first division, positive reactions were obtained with, or without, the pellicle. As the disease progressed the reaction became more intense. The spinal fluids continued to give the test for several days after removal. In one instance, a definitely positive ring was obtained after the fluid had remained in a test-tube for fourteen days.

In analyzing the 12 cases of tuberculous meningitis it was found that the tryptophane test was the first corroborative evidence of the diagnosis in three of the cases, and also in another case not included in the above series because no autopsy was obtained.

Cases

1: Male, aged 52, admitted December 5, 1932, with predominantly fibrotic pulmonary tuberculosis and tuberculous epididymitis. Ambulant and afebrile for two weeks when suddenly developed headache and fever. Spinal puncture performed and the tryptophane test positive. Seven days later exhibited definite neurological signs of meningitis. Tubercle bacilli found in spinal fluid eight days after onset.

2: Female, aged 41, admitted August 8, 1932, with bilateral fibrocaseous pulmonary tuberculosis complicated by right pyopneumothorax. Course active and febrile. Presented no neurological symptoms until February 11, 1933, when began to complain of headache. On February 12, slight nuchal rigidity was observed and, the following day, patient presented right hemiparesis and right hemisensory syndrome. Spinal fluid gave positive Pandy and contained 110 lymphocytes per cmm. No tubercle bacilli found. Tryptophane test positive. Neurological diagnosis rested between cerebral vascular lesion or embolus in region of left middle cerebral artery, and tuberculoma of brain. On autopsy there was found tuberculous meningitis peculiarly localized to left side of brain. Brain itself negative.

3: Male, aged 31, admitted March 4, 1932, with extensive bilateral fibrocaseous pulmonary tuberculosis and marked evidence of generalized amyloidosis including positive Congo-red test. Course uneventful until December 30, 1932, when patient suddenly had convulsive seizure and began to complain of headache. No definite signs of meningitis, but right facial weakness suggested possibility of tuberculoma of left hemisphere. Spinal fluid showed 28 cells per cmm., mostly lymphocytes, and total protein of 70.6. No tubercle bacilli found. Tryptophane test positive. Convulsive onset brought up possibility of uraemia on basis of renal amyloidosis but blood chemistry negative. Eight days after initial symptoms, patient presented frank signs of meningeal involvement. Autopsy showed tuberculous meningitis.

4: Male, aged 35, admitted September 16, 1932, with dominantly fibrotic pulmonary tuberculosis. Course uneventful until January 9, 1933, when disclosed that he had been suffering from headaches for few days. On January 14, changes in patient's mental status were noted. Tryptophane test performed January 15 positive, and on January 17 patient presented characteristic signs of meningitis. Tubercle bacilli never recovered from spinal fluid and no autopsy obtained. However, clinical syndrome and character of spinal fluid were practically pathognomonic of tuberculous meningitis.

Inasmuch as "false positive" reactions are so easily obtained with xanthochromic, purulent, and haemorrhagic fluids it seems advisable not to attempt interpretation of such fluids with the tryptophane test. While there is an appreciable difference between the violet ring obtained in tuberculous-meningitis fluids and the purplish ring obtained in the "false positive" reactions, it is rather precarious to make so important a diagnosis on a slight color change, and particularly so when the exact chemistry of the reaction is not clearly understood. In the final evaluation of the test we have found it to be of definite practical use as a routine procedure in the examination of the spinal fluid. There is very little time consumed and in the absence of xanthochromia, pus and haemorrhage, the reaction is of diagnostic value. On the tuberculosis wards where associated neurological conditions only rarely complicate the situation, the tryptophane test offers a rapid method for establishing the diagnosis of tuberculous meningitis. We agree with Lichtenberg, however, that the test is not to be relied on to the exclusion of the demonstration of the tubercle bacillus or guinea-pig inoculation.

CONCLUSIONS

1. The presence of a positive tryptophane test is strongly suggestive, but not pathognomonic, of tuberculous meningitis.

2. Haemorrhagic, purulent, and xanthochromic fluids give "false positive" reactions which are usually distinguishable from those obtained in tuberculous meningitis by the purplish color. Indistinguishable positive reactions may be obtained with clear spinal fluids in which the protein is increased.

3. There is sufficient evidence to warrant the use of the tryptophane test as a routine procedure in the examination of the spinal fluid.

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THE SIGNIFICANCE OF REPEATED RED-CELL SEDIMENTATION RATE DETERMINATIONS IN PULMONARY TUBERCULOSIS[1]

LOUIS E. SILTZBACH

Nothing is of more importance in the treatment of pulmonary tuberculosis than cognizance of the activity or quiescence of the lesions under consideration. We are only too familiar with those cases which fall into the group of quiescence when judged by our common standards of the trend of the temperature, pulse and weight, but which, on further study of their clinical course, reveal active and progressive lesions. It was with the intent of supplementing our clinical and roentgenographic criteria for the activity of a pulmonary tuberculous lesion that a search was made in the field of blood study for a test which might be auxiliary in this determination. The Erythrocyte Sedimentation Reaction (E. S. R.) was decided upon because of its simplicity, its practicability and its wide acceptance among phthisiologists today.

The history of the E. S. R., as well as its physiological and chemical bases, has been the subject of numerous papers (1) (2) (3). It is the purpose of this communication to confine itself to the correlation of the clinical behavior of pulmonary tuberculous patients with their E. S. R. determinations.

METHODS

The Cutler Graphic E. S. R. method was adopted in this series because of its practicability and accuracy (4). Simultaneous observations were possible on the blood samples of 24 patients.

Briefly, the test may be described as follows: The blood is drawn from a vein into a syringe containing 0.1 cc. of 3 per cent sodium-citrate solution to the 1-cc. mark. The syringe is gently tipped to and fro to ensure thorough admixture, and the contents are introduced into a 1-cc.-capacity sedimentation tube which is calibrated to 50 mm. Readings of the level of the erythrocytic settling are taken every five minutes for one hour and the results are graphically recorded.

[1] From the Montefiore Hospital Country Sanatorium, Bedford Hills, New York.

The curves obtained fall into four general groups (see figure 1). In the first group the red blood corpuscles settle to a level of 10 mm. or less at the end of an hour. This curve is called a *horizontal line* (*H. L.*) and is found in normal individuals. In the second group, the corpuscles settle to a point between the 10- and 20-mm. mark. This curve is called a *diagonal line* (*D. L.*) and is found in patients with pulmonary tuberculous lesions that are either quiescent or mildly active. In the third group, the corpuscles settle to a point below the 20-mm. mark within 30 to 60 minutes. This curve is called a *diagonal curve* (*D. C.*), and is found in patients with pulmonary tuberculous lesions which are moderately to markedly active. In the fourth group, the corpuscles settle to a point below the 20-mm. mark within 30 minutes or less. This curve is called a *vertical curve* (*V. C.*) and is observed in patients with pulmonary tuberculous lesions that are most markedly active.

Each E. S. R. curve may be divided into three stages of sedimentation: (a) the period of aggregation, (b) the period of constant sedimentation, and (c) the period of packing (see figure 1).

The reading of the corpuscular settling level at the end of an hour, expressed in millimetres, is known as the *Sedimentation Index*. The range of the Sedimentation Index for normal individuals lies between 2 and 10 mm., and is slightly higher in females than in males. An index greater than 10 mm. is considered abnormal and, in general, it has been found that the Sedimentation Index increases as the disease becomes more severe.

The Sedimentation Time is the time interval required for the effective settling of the erythrocytes to take place. This point is reached when the rate of erythrocytic settling is less than 1 mm. in five minutes. A Sedimentation Time of less than 30 minutes is found in vertical curves (V. C.); one between 30 and 60 minutes in diagonal curves (D. C.).

The Cutler Graphic Method for E. S. R. determination does not correct for anaemia (5) (6). In a test in which two concomitant conditions may both produce a rapid E. S. R., it is important to determine the influence of each of these two factors on the E. S. R. It is for this reason that the blood-cell volume percentage was determined on the blood samples studied.[2]

[2] Parallel determinations of the blood-cell-volume percentages were made on many of the blood samples, using heparin and 3 per cent sodium citrate as anticoagulants. Heparin was used in these blood-cell-volume studies to estimate the shrinkage effect of the sodium citrate on the erythrocytes. The estimated cell volumes were corrected for this error when sodium citrate was used.

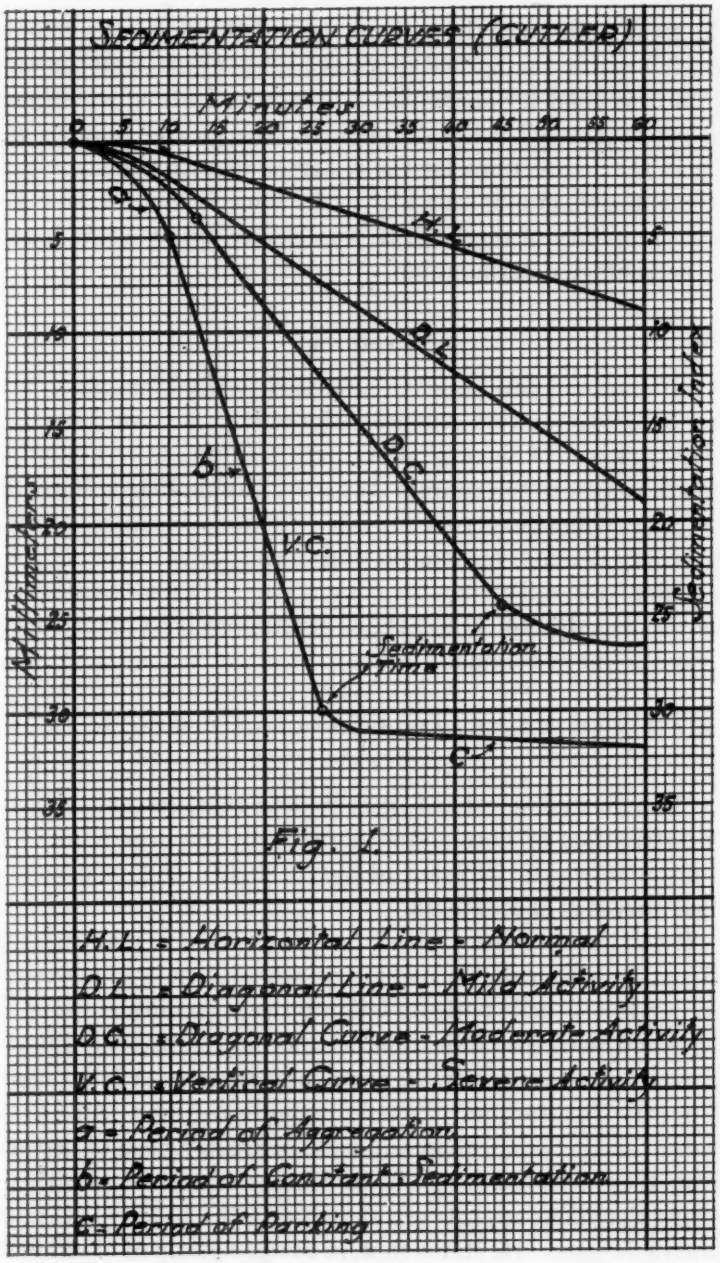
SEDIMENTATION CURVES (CUTLER)
Minutes
0 5 10 15 20 25 30 35 40 45 50 55 60
H.L.
D.L.
D.C.
V.C.
a
b
c
Millimeters
Sedimentation Index
Sedimentation Rate
Fig. 1.
H.L. = Horizontal Line = Normal
D.L. = Diagonal Line = Mild Activity
D.C. = Diagonal Curve = Moderate Activity
V.C. = Vertical Curve = Severe Activity
a = Period of Aggregation
b = Period of Constant Sedimentation
c = Period of Packing

FIG. 1

In the great majority of the patients studied, the blood-cell-volume percentages fell within the normal range (40–48 per cent) and therefore required no correction for anaemia. Of those patients in whom the cell-volume percentage fell below 40 per cent, the greater number were so severely ill that corrections for the anaemia affected the significance of the sedimentation graphs but little. In some instances, however, an unexpected rapidity of the E. S. R. was cleared up by a low blood-cell-volume percentage determination.

RESULTS

Five hundred and two patients, admitted to the Montefiore Hospital Country Sanatorium, were studied with the E. S. R. from June, 1931, to May, 1932. Eight of these patients were suffering from a nontuberculous disease and are excluded from the series, leaving 494 patients who had demonstrable pulmonary tuberculosis. In most instances, tests were repeated every two to three months during the patient's stay at the sanatorium, more frequently when the patient's condition warranted it. Table 1 shows an analysis of 1170 E. S. R. determinations grouped according to the type of curve obtained.

THE RELATION OF AGE, SEX AND DURATION OF DISEASE TO THE E. S. R. CURVE

Age: As indicated in table 1, it is evident that, in each age-group, a similar distribution of normal and abnormal curves are found. In the group of patients over 50 years of age, a slightly higher percentage of abnormal curves is encountered.

Sex: It will be noted from table 1 that 35 per cent of male patients had *E. S. R.* curves within the normal range; whereas, only 13 per cent of the *E. S. R.* curves of female patients fell into the same normal group. This was consistent with the clinical observation of the marked difference in disease activity between the male and female patients at Montefiore Hospital Country Sanatorium. Female patients required more prolonged confinement to the sanatorium and were in greater need of bed-rest and care while they were there. Fishberg (7) has furnished us with a chart illustrating the difference between the sexes in the tuberculosis mortality rate at various ages. He states that, in the age-group of 15–20 years, the mortality in females is twice that in males, and in the age-group of 20–25 years, the mortality rate is more than 40 per cent higher in females than

TABLE 1

Analysis of 1170 E. S. R. determinations in 494 patients with pulmonary tuberculosis

Relation of age, sex and duration of disease to type of E. S. R. curve*

E. S. R. CURVE	TOTAL NUMBER OF READINGS	TOTAL PER CENT	TOTAL** AVERAGE READINGS	TOTAL PER CENT	AGE-GROUPING				
					15–20 years, 51 cases	21–30 years, 199 cases	31–40 years, 109 cases	41–50 years, 92 cases	51 years, 43 cases
					per cent	*per cent*	*per cent*	*per cent*	*per cent*
H. L.	343	29.5	130	26	29	28	30	25	18
D. L.	356	30.0	141	28	29	27	30	30	40
D. C.	363	31.0	186	38	33	38	33	35	40
V. C.	108	9.5	37	8	9	7	7	10	2

E. S. R. CURVE	SEX DISTRIBUTION		DURATION OF DISEASE					
	Males, 307 cases	Females, 187 cases	Less than 6 months, 76 cases	6–12 months, 56 cases	1–2 years, 83 cases	2–5 years, 142 cases	5–10 years, 79 cases	10 years, 58 cases
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
H. L.	35	13	29	27	30	24	20	31
D. L.	29	30	26	27	28	28	30	33
D. C.	31	47	37	39	31	41	44	34
V. C.	5	10	8	7	11	7	6	2

* The E. S. R. curves obtained are grouped according to the Cutler Classification (see text).

** The average E. S. R. curve computed for all readings on each patient.

TABLE 2

Relation of weight-curve, temperature, pulse-rate to type of E. S. R. curve

E. S. R. CURVE	WEIGHT-CURVE				
	Gain more than 10 lbs.	Gain 5–10 lbs.	Stationary	Loss 5–10 lbs.	Loss more than 10 lbs.
	82 cases	108 cases	239 cases	44 cases	21 cases
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
H. L.	27	30	29	14	5
D. L.	38	34	28	7	14
D. C.	31	32	37	52	52
V. C.	4	4	6	27	29

E. S. R. CURVE	TEMPERATURE				PULSE-RATE		
	Normal	99.2°–100°	100°–102°	102°	84 or less	85–100	101 or more
	292 cases	106 cases	73 cases	23 cases	146 cases	272 cases	76 cases
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
H. L.	42	6	0	0	55	23	0
D. L.	37	22	11	0	36	34	4
D. C.	20	68	67	30	9	39	57
V. C.	1	4	22	70	0	4	39

in males. The E. S. R. curves, as well, reflect a greater incidence of abnormal curves in the female group of patients.

Duration of Disease: The duration of the pulmonary-tuberculosis disease process, of itself, apparently does not significantly influence the E. S. R. curves (table 1).

RELATION OF CLINICAL MANIFESTATIONS OF ACTIVITY TO THE E. S. R. CURVE

Weight

The weight-curve of patients has often been used as a criterion for determining the course of the patient's disease process. When one remembers that many patients admitted to sanatoria have been underfed for years, it cannot surprise us to see these patients gain 10 to 15 lbs. on nourishing food and adequate bed-rest after a short time at the sanatorium. This increase in body weight is not always a mirror of the course of the pulmonary disease. A patient may maintain or even gain weight, despite the fact that his tuberculous process continues to spread. From the figures in table 2, it is evident that the group of patients showing gains in weight has a far greater percentage of normal E. S. R. curves than the group showing losses in weight. It must also be noted, however, that a great percentage of patients possessing increasing or stationary weight-curves show a high percentage of abnormal E. S. R. curves.

Fever

Persistent fever in pulmonary tuberculosis is always a sign of activity in the tuberculous lesion but a normal temperature is not necessarily a sign of quiescence or arrest of the lesion. From table 2 it is observed that the presence of fever is accompanied, in all instances, by an increase in the E. S. R. rate. However, a normal temperature is associated with an abnormal E. S. R. curve in 58 per cent of instances. No case with mouth temperature of 99.6° or higher, associated with a normal sedimentation curve, was encountered.

Pulse

Many phthisiologists lay great stress on the importance of tachycardia as an index of activity in pulmonary tuberculosis. In table 2, the marked increase in incidence of abnormal E. S. R. curves as the pulse-rate increases is striking. No vertical curves (V. C.) were encountered in patients with pulse-rates of 85 or less; nor were normal E. S. R. curves

seen in cases whose pulse-rate exceeded 100. In comparing the figures for tachycardia and fever in table 2 it is seen that abnormal E. S. R. curves are less frequently observed in patients with a normal pulse-rate than in patients with normal temperatures (45 per cent abnormal curves with normal pulse; 58 per cent abnormal curves with normal temperature).

RELATION OF TYPE OF LESION, EXTENT OF LESION, POSITIVE SPUTUM AND CAVITATION TO E. S. R. CURVE

Type of Lesion

It is extremely difficult to correlate the E. S. R. curve of a patient with his type of pulmonary tuberculosis owing to difficulties in classification and gradation of the types and severity of the lesions. However, by dividing the cases arbitrarily into three groups, that is, exudative type, fibroid type and mixed type, it is found, as shown in table 3, that the vertical and diagonal E. S. R. curves indicative of rapid sedimentation rates occur with much greater frequency in the acute or exudative type than in the fibroid type. In the fibroid type the vertical curve was not found in any instances.

Extent of Lesion

Though it is true that an exudative lesion involving a part of one lobe may cause a more rapid E. S. R. curve than a widely-distributed, densely-fibrotic lesion, the observations recorded in table 3 are not in accordance with the generally-accepted opinion that there is a complete lack of correlation between the E. S. R. curve and the extent of the pulmonary tuberculous lesion.

It is evident from this table that, the greater the lung area involved in the disease process, the more frequently are abnormal E. S. R. curves encountered.

Sputum

It is clear from table 3 that the patients with sputum containing tubercle bacilli registered vertical curves (V. C.) and diagonal curves (D. C.) approximately five times as frequently as patients with sputum containing no demonstrable tubercle bacilli or having no sputum. The normal E. S. R. curve, on the other hand, occurs in the former group approximately only one-fifth as frequently as in the latter group. The only instances of a vertical curve (V. C.) found in three patients who had

sputum negative for tubercle bacilli, or who had no sputum, occurred in the presence of generalized miliary tuberculosis as confirmed by autopsy. It is an interesting fact that, with the disappearance of the tubercle bacilli from the sputum, there is a concomitant change in the E. S. R. curve toward the normal. Individual serial determinations on a small group of patients when their sputum was positive and later negative confirm this observation.

TABLE 3

Relation of extent of lesion, type of lesion, positive sputum and cavitation to type of E. S. R. curve

E. S. R. CURVE	EXTENT OF LESION (LUNG AREA INVOLVED)					
	1/6 lung area	1/4 lung area	1/3 lung area	1/2 lung area	2/3 lung area	All lobes
	98 cases	69 cases	82 cases	113 cases	93 cases	39 cases
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
H. L.	67	33	23	15	4	10
D. L.	27	43	45	26	15	15
D. C.	6	24	31	54	56	52
V. C.	0	0	1	5	25	23

E. S. R. CURVE	TYPE OF LESION			SPUTUM		CAVITATION	
	Exudative	Fibroid	Mixed	Positive for tubercle bacilli	Negative for tubercle bacilli*	Positive	Negative
	253 cases	152 cases	89 cases	302 cases	192 cases	335 cases	159 cases
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
H. L.	12	56	13	10	52	12	59
D. L.	25	33	32	28	34	32	31
D. C.	51	11	49	49	12	44	8
V. C.	12	0	6	13	2	12	2

* Sputum is recorded as negative for tubercle bacilli when at least four routine examinations and one antiformin concentration examination fail to reveal the organisms.

Cavitation

Table 3 indicates that the diagonal and vertical E. S. R. curves occur approximately six times as frequently in patients with cavitation as in patients without cavitation. The normal E. S. R. curve, on the other hand, occurs only one-fifth as frequently in these patients with cavitation as in those without any evidence of cavitation. It is noteworthy that all three instances of a vertical curve (V. C.) in the absence of cavitation occurred in patients suffering from generalized miliary tuberculosis as

confirmed by autopsy. These observations are consistent with the clinical observations that the formation of cavities in tuberculosis is associated with continued activity of the lesion.

ARTIFICIAL PNEUMOTHORAX

Many observers have found the E. S. R. determination of great use in guiding themselves as to the course of disease in a collapsed lung (8). Thirty-six pneumothorax patients were studied during the year before pneumothorax was induced and at frequent intervals after induction, in conjunction with clinical and roentgenographic observations. The patients were divided into two groups, those with effective collapse and those with ineffective collapse. Effectiveness of collapse was determined clinically by the amelioration and abatement of constitutional and local symptoms, as well as the disappearance of tubercle bacilli from the sputum (in unilateral cases), and roentgenographically by collapse of the diseased part of the lung. By these criteria, collapse was considered effective in 15 patients and ineffective in 21 patients. It must be added that in the patients showing ineffective pulmonary collapse, a palliative influence was obtained in the majority of instances, which justified the continuation of the pneumothorax treatment. The E. S. R. determinations were studied at various time-intervals during the course of the collapse therapy, and the average change in millimetres of the sedimentation index at these time-intervals was plotted for both effective and ineffective collapse cases. From figure 2 it is evident that, with the establishment of effective pulmonary collapse with pneumothorax, the sedimentation index of the E. S. R. rapidly diminishes toward the normal level.

It is to be noted that the greatest improvement in the E. S. R. in the effectively collapsed cases takes place within one month after the induction of the pneumothorax. During the second month, however, little or no change in the sedimentation index is observed. In the subsequent four months of treatment, a steady decline of the sedimentation index toward the normal level is again observed. Six months and longer after the induction of the collapse, no further change is noted in the sedimentation index. The composite curve of the ineffectively collapsed cases, as shown in figure 2, illustrates the striking difference between the behavior of the E. S. R. in this group of cases and that of the effectively collapsed cases.

The problem of voluntary discontinuation of artificial-pneumothorax

therapy and of the extent of healing in a reëxpanding lung has been constantly with us since the advent of this form of therapy. This problem is not very often met with at the Montefiore Hospital Country Sanatorium because of the necessity of discharging patients before such a stage

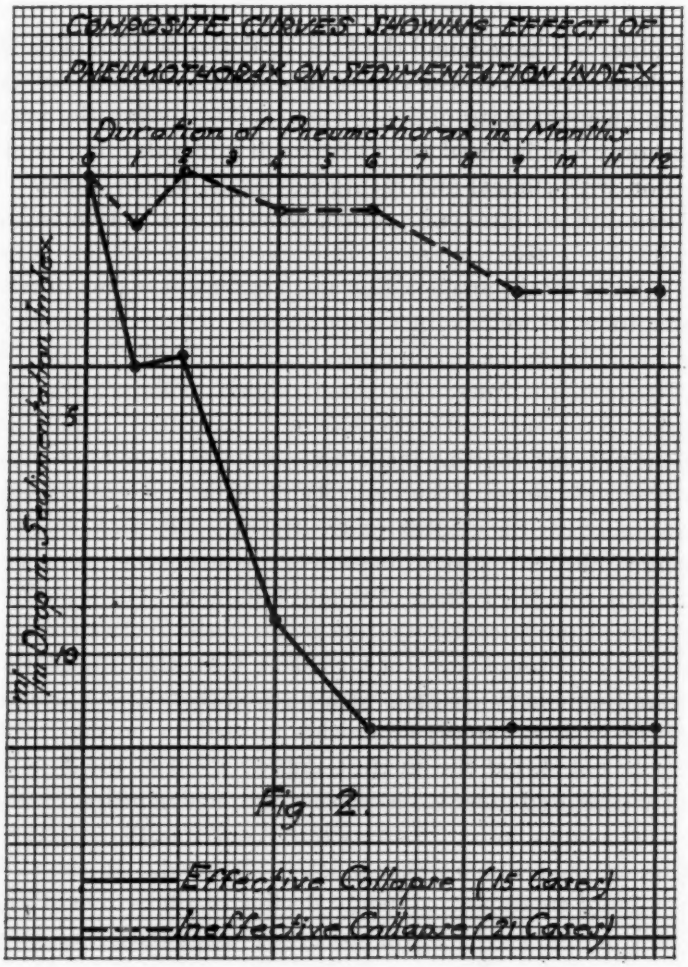
Composite Curves Showing Effect of
Pneumothorax on Sedimentation Index
Duration of Pneumothorax in Months
1 2 3 4 5 6 7 8 9 10 11 12
Mm. Sedimentation Index
5
10
Fig 2.
Effective Collapse (15 Cases)
Ineffective Collapse (21 Cases)

FIG. 2

is reached. One instance which came under observation illustrates in its limited way the value of the E. S. R. determination in this problem.

J. A.: Female, 28, was admitted to the Montefiore Hospital Country Sanatorium from another institution where she had received pneumothorax therapy

which required very high positive intrapleural pressures to maintain a collapse of her diseased lung. On admission her E. S. R. curve was of the diagonal-line type with a sedimentation index of 13 mm. Her left lung was found almost completely collapsed and, because of the high positive intrapleural pressures and marked mediastinal displacement to the opposite side, it was decided to withhold inflations for a two-week period. At the end of this time, the patient's E. S. R. curve became a diagonal curve with a sedimentation index of 22 mm. On fluoroscopy a moderate reëxpansion of the collapsed lung was visible. Two days later the patient began to complain of increased local and constitutional symptoms. Her collapse was reinduced with positive intrapleural pressure but the patient left the Sanatorium soon afterward of her own volition, making further study impossible for the time. This patient was again seen in a follow-up clinic three months after her discharge. She reported that she was still receiving pneumothorax therapy at an out-patient clinic with high positive pressure still necessary to keep her lung collapsed. She was well enough to do office work and was free from all symptoms. Fluoroscopy revealed a complete collapse and her E. S. R. curve was again a diagonal line with a sedimentation index of 15 mm.

It is thought that repeated E. S. R. determinations may be of special value as a means of following the disease activity of a collapsing lung as well as of a reëxpanding one.

Pneumothorax-treated patients with contralateral involvement reflected a lesser improvement in their E. S. R. curve than unilateral cases, probably as a result of persistently active foci in the untreated lung. Pneumothorax patients showing disappearance of tubercle bacilli from the sputum reflected greater improvement in their E. S. R. curves than those patients whose sputum remained persistently positive for bacilli.

COMPLICATIONS

Pleural effusions were associated with a rise in the E. S. R. value in most instances. There were several instances, however, of small to moderate homolateral exudates complicating pneumothorax therapy in which no change in the E. S. R. value was present. Rupture of the lung with resultant pyopneumothorax occurred in three patients during the course of pneumothorax therapy. In all instances, a vertical curve (V. C.) was observed after the rupture of the lung had occurred.

Tuberculosis of the Larynx

This complication was observed in 10 per cent of the patients studied. Table 4 shows that 70 per cent of these had diagonal curves and vertical

curves for their E. S. R. graph. In comparing these figures with those for average curves of all patients, as shown in table 1 (46 per cent of D. C. and V. C., E. S. R. curves), it is seen that, in the presence of this complication, an E. S. R. curve indicative of disease activity occurs with much greater frequency. In some of the instances of tuberculous laryngitis, the laryngeal lesion was fibrotic and healing, and frequently in these instances the normal E. S. R. curve was recorded.

Tuberculosis of the Intestines

All patients suffering from tuberculosis of the intestines showed a D. C. or a V. C. sedimentation curve (table 4).

TABLE 4

Relation of complications, tuberculous and nontuberculous, to the type of E. S. R. curve

E. S. R. CURVE	TUBERCULOSIS OF LARYNX	TUBERCULOSIS OF INTESTINE	DIABETES AND PULMONARY TUBERCULOSIS
	50 cases	14 cases	13 cases
	per cent	*per cent*	*per cent*
H. L.	12	0	7
D. L.	18	0	7
D. C.	56	64	86
V. C.	14	36	0

Extrapulmonary Tuberculosis

In all instances of extrapulmonary tuberculosis (bone, joint, genitourinary tract, meninges and peritoneum) associated with active pulmonary tuberculosis, the E. S. R. was markedly increased when compared with cases without these complications.

Haemoptysis

The relation of haemoptysis to the E. S. R. was studied in 17 instances before and after the onset of the process. It was found that haemoptysis, *per se*, does not change the E. S. R. value unless it is followed by an extension of the tuberculous disease process.

Nontuberculous Complications

Thirteen patients suffering with the combined diseases of pulmonary tuberculosis and diabetes mellitus were studied. In table 4 it can be seen that, in the diabetic tuberculous patient, the E. S. R. has a tendency

to be more rapid than in tuberculous patients without this complication. In the patients studied, no apparent relation could be discerned between the E. S. R. values and the height of the glucose content of the blood or the intensity of insulin therapy. The rapid E. S. R. rates obtained were probably a reflection of the greater severity and of the exudative character of the tuberculous disease process in these diabetic patients.

Superimposed, acute, infectious processes (tonsillitis, appendicitis, gonorrhoea, etc.) associated with constitutional response materially increase the rapidity of the E. S. R. in patients with pulmonary tuberculosis.

Six family groups confined to the Montefiore Hospital Country Sanatorium during the year were studied to determine whether there was any similarity in the E. S. R. curves among the members of each family group. In the series there were three members in one family and two members of the five remaining families.

E. S. R. Curves in Six Family Groups

1:	Brother DC	*4:*	Brother DC
	Brother DL		Brother DC
	Sister DC		
2:	Brother HL	*5:*	Father DC
	Brother HL		Son DL
3:	Sister DC	*6:*	Brother DC
	Sister DC		Sister DC

It is of interest to note that, in members of the same immediate family who are suffering from pulmonary tuberculosis, there is a tendency toward similarity of E. S. R. values.

PROGNOSIS

Two hundred and sixty-three of the discharged patients were followed and reëxamined four to 12 months after discharge. Of these, the E. S. R. was determined in 130 instances. The condition of patients after discharge is grouped roughly into (1) those who were well enough to carry on daily activity, (2) those confined to bed, and (3) those who had died.

It is readily observed from table 5 that there is a definite correlation between the E. S. R. curve and the course of the pulmonary tuberculous disease after discharge from the sanatorium. Ninety-seven per cent of

those patients showing a normal H. L. curve at the time of discharge from the sanatorium remained well during the subsequent year; whereas 46 per cent of those patients discharged with a V. C. curve died in this same period. The close correlation between the clinical behavior of the tuberculous patient four to twelve months following discharge and his E. S. R. curve recommends the test for use as an index of the patient's suitability for cessation of treatment. Further observations on these patients at the two-, three- and five-year periods after discharge will illustrate more fully the degree of permanency of the E. S. R. test's prognostic value.

TABLE 5

*Relation of the type of E. S. R. curve on discharge from sanatorium to condition of patient 4 to 12 months after discharge**

CONDITION AFTER DISCHARGE	DISCHARGED WITH H. L.	DISCHARGED WITH D. L.	DISCHARGED WITH D. C.	DISCHARGED WITH V. C.
	117 cases	54 cases	58 cases	24 cases
	per cent	*per cent*	*per cent*	*per cent*
Well	97.2	74.3	12	0
Sick	2.0	22.0	76	54
Dead	0.8	3.7	12	46

* Many of our patients are transferred at the time of discharge to Montefiore Hospital for further medical care. These patients, as well as patients who left the sanatorium contrary to medical advice, are included among the discharged patients in this table.

STABILITY OF THE E. S. R. FOLLOWING DISCHARGE

Table 6 presents a record of the stability of the various types of E. S. R. curve as studied in 130 patients within the year after their discharge from the sanatorium. The E. S. R. curve on the date of discharge is compared with the E. S. R. curves obtained during the 4- to 12-month period after discharge. The relative stability of the horizontal line (H. L., the normal curve) and that of the vertical curve (V. C., the most severe type) is to be contrasted with the lability of the two intervening types of curves, the diagonal line and the diagonal curve; thus, if a patient left the sanatorium with a normal horizontal line (H. L.) curve, he retained that E. S. R. curve for 4–12 months following discharge in 90 per cent of instances. In the group of patients leaving the sanatorium with a vertical curve, all who were still alive retained that type of curve during the year after discharge. However, if the patient left the sanatorium with a diagonal line (D. L.) or a diagonal curve (D. C.), the possibilities of shifting to a better

or worse group of E. S. R. curves, or retaining the same curves, were approximately evenly divided.

TABLE 6

Stability of E. S. R. curve of 130 patients 4 to 12 months after discharge from sanatorium

E. S. R. CURVE 4–12 MONTHS AFTER DISCHARGE	DISCHARGED WITH H. L.	DISCHARGED WITH D. L.	DISCHARGED WITH D. C.	DISCHARGED WITH V. C.
	60 cases	35 cases	30 cases	5 cases
	per cent	*per cent*	*per cent*	*per cent*
H. L.	90.0	43.0	10	0
D. L.	8.5	28.5	20	0
D. C.	1.5	22.5	53	0
V. C.	0	6.0	17	100

DISCUSSION

From the data presented in this communication, it will be observed that the E. S. R. determination is of special value in the treatment of pulmonary tuberculosis in that it offers a simple numerical expression of the activity of the disease process. Its sensitive reflection of any fluctuation in the severity of the disease activity makes the E. S. R. reaction an excellent prognostic barometer, which in numerous instances warns the clinician of an approaching breakdown long before the patient exhibits any untoward constitutional or local symptoms. In the several instances in which the clinical opinion was at variance with the E. S. R. findings, the further clinical course generally corroborated the findings of the blood observations.

In examining the E. S. R. curves presented in table 3 grouped under the headings, *Exudative Lesions*, *Positive Sputum* and *Pulmonary Cavitation*, it is found that 10–12 per cent of these fall into the H. L. (normal) E. S. R. curve group, despite these rather presumptive evidences of the presence in the patient of an active disease process. In analyzing these normal E. S. R. curves, it was noted that their sedimentation indices almost always approached the upper limit for the normal group, that is, 8–10 mm. However, this indistinct boundary between the upper limit of the normal E. S. R. curve and the lower limit of the abnormal curves presented but temporary difficulties, for, on repetition of the E. S. R. blood determinations, a migration of the sedimentation index to a lower level within the normal (H. L.) group when improvement took place (the more common occurrence) or to a higher level into the abnormal

groups (D. L., D. C., V. C.) when relapse was the outcome, generally obviated the difficulty encountered. With an appreciation of the slight overlapping between the normal and abnormal E. S. R. curves and of the necessity for repeated determinations, the value of the test as a measure of disease activity is materially increased.

In the treatment of pulmonary tuberculosis by pneumothorax-collapse therapy, the therapeutic effect of such treatment is accurately reflected in the patient's E. S. R. curve and until the curve returns from the abnormal to the normal level, destruction of tissue has not subsided and further treatment is indicated. The test is occasionally of more limited value in pneumothorax patients with contralateral involvement, since the continued disease activity in the untreated lung may have a tendency to obscure the recording of a favorable trend in the collapsed lung.

That the E. S. R. determination is of prognostic value is illustrated in table 5. A patient whose E. S. R. curve returns to normal from a D. C. or D. L. curve is far more likely to improve and become well than a patient whose curve does not make this change. Likewise, the appearance of a V. C. curve in the course of the disease almost invariably presages a prolonged disease period, if not a fatal outcome. These facts make the E. S. R. test especially useful in observing the progress of the pulmonary disease process of a patient both in and out of the sanatorium. The relative stability and favorable prognostic significance of the normal E. S. R. curve (H. L.) after discharge of a patient from treatment makes the attainment of the H. L. normal curve before discharge a most desirable one.

The value of repeated E. S. R. curves of a patient with tuberculosis during active treatment and in follow-up clinics suggests its routine use in sanatorium and office practice.

SUMMARY AND CONCLUSIONS

The E. S. R. curves (Cutler) were studied on 494 patients with pulmonary tuberculosis: 1170 individual tests were performed. The data so obtained were analyzed, and correlative studies with the constitutional and local manifestations of the disease were made. It was found that curves reflecting moderate and severe activity occur with greater frequency in patients with fever, rapid pulse, loss of weight, positive sputum, cavity-formation, extensive lesions, and extrapulmonary tuberculosis. The E. S. R. curve reflects the progress of the disease and a change in E. S. R. curve often precedes the change in clinical symptoms and signs.

It is of value, therefore, in prognosis in pulmonary tuberculosis. In collapse therapy the E. S. R. may be utilized as a gauge of the effectiveness of the treatment. The use of E. S. R. curve determinations in routine sanatorium and private practice in tuberculosis is recommended.

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THE ERYTHROCYTE-SEDIMENTATION TEST[1,2]

With Special Reference to Tuberculosis

A. R. MASTEN

The erythrocyte sedimentation test is perhaps the simplest and most accurate of all laboratory procedures for determining the presence of destructive disease. It is based upon the fact that if blood is prevented from coagulating, the red blood corpuscles settle with a different rate in different physiological and pathological conditions. The presence of a destructive process in the body increases the rapidity with which the red cells settle, the rate of fall being a measure of the intensity of the process. The sedimentation rate therefore is nonspecific; it merely indicates the presence or absence of a destructive process.

Cutler (1) maintains that the sedimentation test should be used much more extensively than it is at present because a rapid rate always indicates the presence of serious disease. The one exception to this is pregnancy which is the only physiological process that is accompanied by an increased rate. Thus, he says, the test serves as an accurate diagnostic lead. Cutler also believes that the sedimentation rate is a more accurate gauge of the intensity of the disease process than fever, pulse-rate or the leucocyte count, and therefore serves as a valuable prognostic index. All investigators are not so enthusiastic as Cutler about the sedimentation test, but the majority now agree that it is of value. A recent editorial in the *Journal of the American Medical Association* (3) states that "there seems little doubt that the blood-sedimentation test is of some value in the recognition, prognosis, and course of certain systemic diseases."

The exact nature of the sedimentation reaction has not been definitely shown although most investigators believe that it is due largely to changes in the viscosity of the blood-plasma resulting from variations in its fibrinogen and globulin content (3). There are several accessory factors, however, which are thought to influence the sedimentation rate to a certain extent. Among these are anaemia, haemoglobin content of

[1] From the Lutheran Sanitarium, Wheat Ridge, Colorado.

[2] Read at a meeting of the Denver Sanatorium Association, Denver, Colorado, May 23, 1933.

red-cells, the acid-base equilibrium of the blood, the surface tension of the plasma, the electrical charge of the red-cells, and the color index. Rourke and her co-workers (5) (6) believe that anaemia is such an important factor that it must be corrected for, if an accurate sedimentation rate is to be obtained. Westergren (7) also believes that the haemoglobin content of the blood can be determined from the sedimentation rate and has constructed a chart for this purpose. Whatever the exact nature of the reaction, it is now generally agreed that it depends upon the amount of cellular destruction going on in the body; the greater the destruction, the faster the rate.

Several different techniques have been developed for performing the sedimentation test. The principal methods now used are those developed by Westergren (7), Linzenmeier (8), Cutler (2), and Rourke (5). All appear to give excellent results when used correctly, although their multiplicity causes some confusion when comparisons among the various methods are attempted. A modified Westergren technique, as described by Morriss (9), was chosen for our work at the Evangelical Lutheran Sanitarium because it was simple, gave a high column which was easy to read, used a small amount of blood, and also did not require the purchase of any new material since all the apparatus is regular laboratory equipment. By this method 1.6 cc. of blood is drawn up into a syringe containing 0.4 cc. of 3.8 per cent sodium-citrate solution. The syringe is gently shaken to mix thoroughly the blood and citrate solution. Exactly 1 cc. of the mixture is then transferred to a graduated 1-cc. pipette which is placed in an upright position in a rack having a rubber base and rubber covered spring-caps to hold the pipette in position. The height of the column of clear plasma above the red-cells is read on the pipette scale at one-, two- and twenty-four-hour intervals. As Westergren points out, the one- and two-hour readings must be made on the minute but an hour or so makes very little difference in the 24-hour reading. In our work, it was found that the two-hour reading offered the best single measure and in this paper it is the two-hour reading that is referred to unless otherwise stated. These readings represent the fall of erythrocytes in percentage of the total blood-volume for a given period of time.

The normal standard for this method has been determined by Morriss and found to be a fall of not more than 10 per cent for the two-hour period. We verified this with tests made on 12 healthy men and women

and 11 patients in whom we could find no evidence of infectious or destructive disease.

As a diagnostic lead and a means of checking a diagnosis arrived at by other means, we have found the sedimentation test to be of considerable value. Since we began the use of the sedimentation test in May, 1930, we have admitted 21 patients on whom we could not confirm a preëntrance diagnosis of pulmonary tuberculosis. In these cases which will be discussed first in this paper, it was reassuring to have the sedimentation rate confirm our final diagnosis.

One particularly annoying case was finally diagnosed as chronic infectious arthritis. The sedimentation rate showed a 25 per cent fall in two hours, which is a moderate increase. Although this rate, of course, does not rule out tuberculosis it was helpful, since it agreed with the sedimentation rates found by other investigators in studying infectious arthritis. In studying the sedimentation rate in arthritis, Cecil (10) found it to be of distinct value in separating arthritis of the infectious type from degenerative changes of the joints as well as from traumatic or postural disturbances. Weiss (11) points out that in acute rheumatic arthritis the sedimentation rate is always increased, while in secondary arthritis it remains normal. He also believes that the rate serves as an important means of measuring the effectiveness of a given therapeutic procedure because the rate does not return to normal until the cause of the arthritis has been removed. It likewise is of great importance in determining when the treatment should be discontinued, because in many instances the rate does not return to normal till as long as seven weeks after the disappearance of symptoms.

One of our patients was found to have syphilis as well as tuberculosis. She showed a marked sedimentation rate, 55.6 per cent. This rate decreased rapidly following antisyphilitic treatment; in a month it was only 27.7 per cent. This last rate probably is a more accurate measure of the activity of her tuberculosis. This result agrees with work done with the sedimentation test in syphilis since active syphilis causes an increased rate. Cutler (1) believes that the sedimentation rate offers an effective means of detecting active syphilis in cases in which a diagnosis might otherwise be missed. He mentions 35 cases which were diagnosed as healthy after a first examination at the Henry Phipps Institute, but who showed an increased rate, and on reëxamination were found to have active syphilis. In this connection, Danzer (12) maintains that the sedimentation test is important in diagnosing syphilitic aortitis, the

diagnostic triad of this disease being angina pectoris, a negative carotid sinus (vagus) reflex and a rapid sedimentation rate.

Another patient who presented very indefinite symptoms was finally diagnosed as having mild hyperthyroidism. The basal metabolic rate on her first test was very high but on the second test was normal. Her sedimentation rate was normal (8 per cent). Another patient with a definite hyperthyroidism also had active pulmonary tuberculosis. Her sedmentation rate was high but improved following thyroidectomy. These findings agree very well with those found by other workers since it has been shown that hyperthyroidism increases the sedimentation rate (13).

In our series of patients we found two cases of Hodgkin's disease. Both of these showed extremely high sedimentation rates, one of 70 per cent and the other of 54 per cent. This confirms the general observations which indicate that the sedimentation rate is definitely increased in malignant tumor, the increase being proportional to the extent of the disease (14).

Three cases of acute appendicitis were found. Two of these were employees at the sanatorium and were presumably healthy. Both of them showed a two-hour reading of 20 per cent, that is, a fall of at least 10 per cent below normal. The other case was one of our tuberculosis patients who had had a sedimentation test made a few days before developing appendicitis. Following the diagnosis of appendicitis, the test was repeated and showed a 15 per cent increase.

Five patients were found to be suffering from functional mental disorders instead of tuberculosis. All showed a normal or practically normal sedimentation rate, that is, 3, 4, 4, 8, and 11 per cent respectively. The normal sedimentation rate in these cases ruled out the presence of active tuberculosis and confirmed our diagnosis of a functional mental disorder, for investigators (15) in mental disease have shown that the sedimentation rate is normal in functional mental disorders, such as nervous exhaustion, anxiety neuroses, hysteria, depression psychoses and the morbid-fear group, while it is increased in those disorders of organic origin. In this field the sedimentation rate is of great value in ruling out organic disease.

Investigations with the sedimentation test have shown that allergic conditions such as bronchial asthma and hay-fever do not influence the sedimentation rate. In our series, there was one case of asthma. On entrance, this patient showed a normal sedimentation rate which by it-

self made us suspicious of the preëntrance diagnosis of pulmonary tuberculosis. Further examination confirmed our suspicions and proved the case to be one of uncomplicated bronchial asthma.

As stated in the first part of this report, certain investigators have believed the sedimentation rate to be influenced by various factors, as, for instance, the red-cell count, the haemoglobin content and the color index of the blood. In order to investigate this asserted relationship between the sedimentation rate and each of these factors, an intensive study was made of 100 consecutive patients.

These patients were grouped according to their red-cell count: 46 were found to have between 4½ and 5 million red-cells per cmm. of blood. In these the two-hour sedimentation rate ranged from 3.6 to 57.8 per cent. A similar variation occurred in the group which had between 4 and 4½ million red-cells. In this group there were 40 patients with two-hour rates ranging from 3.8 to 64.5 per cent. The remaining 14 patients fell into groups too small for any conclusions to be drawn.

In regard to the haemoglobin content of the blood it was found that 89 patients fell into three groups which had a haemoglobin content of 70–79, 80–89, and 90–100 per cent respectively. The sedimentation rates in these three groups varied markedly, the first ranging from 3.8 to 62.8 per cent, the second from 6.7 to 55.6 per cent and the third from 3.6 to 50 per cent.

The sedimentation rates and the color index likewise showed a marked range. Sixteen of the 100 patients had a color index of 1. These showed two-hour sedimentation rates of from 3.6 to 62.8 per cent. Forty-six patients had a color index of 0.9. In these the sedimentation rates ranged from 3.6 to 55.6 per cent. In the group with a color index of 0.8 there were 28 patients who showed sedimentation rates of from 4.2 to 64.5 per cent. The remaining 10 patients were divided between the groups having a color index of 0.7 and 0.6. These groups were too small to warrant any conclusions. Thus, so far as could be determined, no constant relationship existed between the sedimentation rate and any of these factors.

The temperature curve is likewise said to influence the sedimentation rate and this relationship was studied in 174 cases without finding any definite correspondence, although the majority of patients who ran a definitely high temperature also had a correspondingly high sedimentation rate. There were so many exceptions to this, however, that it was found impossible to predict in any particular case the sedimentation

rate from the temperature curve or *vice versa*. The effect of temperature on the sedimentation test was further studied in 25 cases in which the temperature was taken at the same time that the sedimentation test was made. In these 25 cases, no constant relationship could be established. To examine the effect of temperature more closely, a few patients who ran high afternoon temperatures were tested twice on the same day, once in the morning when their temperatures were normal and again in the afternoon when their temperatures were 100 or more. In all cases thus tested the two-hour reading was the same for both tests although the one- and twenty-four-hour readings varied slightly (2 to 4 per cent).

The value of the sedimentation test in determining the course of tuberculosis was studied in a group of 67 patients having definite tuberculosis. In 61 of these patients, the sedimentation rate ran parallel to the clinical course as determined by symptoms and X-ray findings. In 6 cases there was disagreement, but in each of these the change in the patient's condition was slight and it is probable that the sedimentation rate really gave the correct state of affairs. From this, it is evident that the sedimentation test is an accurate method of determining the activity of tuberculosis.

As a means of determining the amount of tuberculous involvement we found the sedimentation rate to parallel more closely the X-ray findings than the results from any other test. Yet even here there was disagreement. This variation was particularly noticeable in the moderately advanced group. The sedimentation test thus appears to measure the degree of activity and not the amount of involvement.

As a means of prognosis we have not found the test to be of exceptional value. Nevertheless, it indicates disease activity quite accurately; thus a high reading is of grave significance. In this connection it is interesting to note that of the 16 patients of this series who died in the sanatorium 14 had a two-hour reading of 34.3 per cent or more on entrance and that the two exceptions developed even higher readings before death. In a few instances, however, patients with an entrance reading as high as 46.7 per cent improved markedly. One such case was discharged as arrested. At discharge, he had a two-hour reading of 15 per cent.

CONCLUSIONS

1. The sedimentation rate is of value in determining the presence of definite destructive disease.

2. This test offers a quick and accurate means of estimating the activity of any destructive disease.

3. It gives an accurate means of estimating the course of tuberculosis.

4. It is a useful if not entirely accurate method for making a prognosis at the first examination of a tuberculous patient.

5. As far as could be determined from this study there was no definite relationship between the sedimentation rate and such factors as the red-cell count, the haemoglobin, and the color index of the blood.

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